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ORGANIC SYNTHESSES

AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

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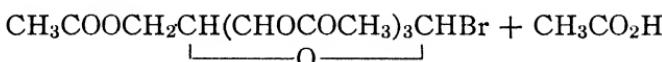
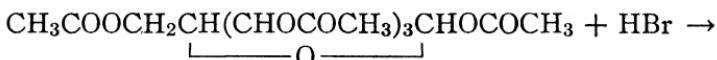
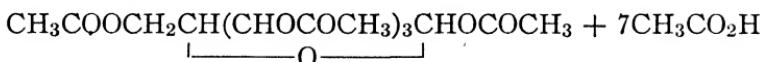
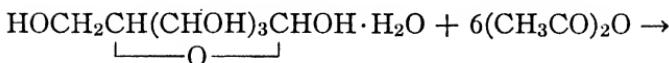
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ACETOBROMOGLUCOSE

(2,3,4,6-Tetraacetyl- α -d-glucopyranosyl Bromide)



Submitted by C. E. REDEMANN and CARL NIEMANN.

Checked by LEE IRVIN SMITH, R. T. ARNOLD, and IVER LEROHL.

1. Procedure

IN a 1-l. round-bottomed flask are placed 66 g. (0.33 mole) of *d*-glucose monohydrate (Note 1) and 302 g. of 95 per cent acetic anhydride (280 cc., 2.81 moles). To this mixture three small drops of concentrated sulfuric acid are added *from a medicine dropper* (Note 2). The glucose is kept in partial suspension by shaking the flask with a swirling motion; the reaction starts almost immediately. If the temperature of the mixture approaches the boiling point, the flask is momentarily immersed in a pan of cold water. Within ten to fifteen minutes nearly all the glucose will have dissolved and the temperature of the reaction mixture will have risen nearly to 100°. The flask is loosely stoppered and is heated on a steam bath for two hours. Then about 200 cc. of mixed acetic acid and acetic anhydride is removed by distillation under reduced pressure (Note 3).

Sixty-five grams (60 cc., 0.64 mole) of acetic anhydride is added to the warm, viscous, light yellow syrup; the mixture is warmed slightly and is mixed by imparting a swirling motion to the flask until the solution is homogeneous. The flask is then fitted with a two-holed rubber stopper bearing an inlet tube and an exit tube, the former reaching within 5 mm. of the bottom.

Dry hydrogen bromide is passed into the mixture, while it is cooled in an ice bath, until the gain in weight is 140–160 g. (Note 4). The flask is then sealed with a rubber stopper and allowed to stand at 5° overnight.

The hydrogen bromide, acetic acid, and acetic anhydride are then removed from the straw-yellow solution by distillation under reduced pressure; a water bath whose temperature does not exceed 60° should be used to heat the mixture (Note 5). During the distillation the solution becomes slightly darker. When no further distillate comes over, or when the residue crystallizes, distillation is stopped, 250–300 cc. of dry isopropyl ether is added (Note 6), and the flask is warmed carefully on a water bath to hasten solution of the product (Note 7). The hot solution is transferred to a 1-l. Erlenmeyer flask and is cooled rapidly, with cold water, to about 45°. The mixture is then allowed to cool slowly to room temperature and is finally placed in a refrigerator at 5° for two or more hours. The acetobromoglucose is collected on a Büchner funnel, pressed into a firm cake, and washed with about 50 cc. of dry isopropyl ether. The white crystalline material, after drying *in vacuo* over calcium (or sodium) hydroxide, weighs 110–120 g. (80–87 per cent of the theoretical amount) (Note 8).

2. Notes

1. Ordinary commercial glucose monohydrate (Cerelose, Clin-tose, etc.) was used.
2. If any uncertainty exists about the size of the drops, it is better to add two drops at first and then to wait at least ten minutes before adding the third drop. If too much sulfuric acid is added the reaction may become so vigorous that it cannot be controlled.
3. The lowest pressure attainable with a good aspirator is satisfactory. The acetic acid may be removed rapidly at bath temperatures up to 100°. Two hundred cubic centimeters of distillate is collected in about thirty-five minutes. Complete removal of the acetic acid is not necessary; the only purpose of removing it is to decrease the amount of hydrogen bromide required.

4. Hydrogen bromide may be generated by dropping liquid bromine into boiling tetrahydronaphthalene, or catalytically from hydrogen and bromine (Org. Syn. 15, 35). Free bromine should be removed from the gas by passing it over red phosphorus. The hydrogen bromide may be passed in very rapidly at first, but as the solution becomes more concentrated the rate of introduction of the gas must be decreased. The absorption of 140 g. of hydrogen bromide requires about two hours if the solution is well stirred; otherwise a longer time is required.

5. This distillation is best conducted in the following manner: The hydrogen bromide is removed as completely as possible at a bath temperature of 40–50° under the pressure attainable with a good aspirator; this requires about one hour. The bath temperature is then slowly increased to 50–60° over a period of about half an hour, during which time considerable acetic acid and acetic anhydride are removed. The receiver is then emptied and the system is connected to a mechanical pump capable of maintaining a pressure of less than 5 mm. By keeping the temperature of the bath at 55–60°, sufficient acetic acid and anhydride are removed in one-half to three-quarters of an hour. The mechanical pump must be adequately protected; the vapors should be passed through a trap cooled in carbon dioxide-alcohol, then through a 12- to 16-in. tower of flake sodium hydroxide, before they enter the pump. A somewhat higher bath temperature can be used with a good aspirator alone, but this will produce much darkening of the reaction mixture and will give a less desirable product.

6. Isopropyl ether which has been in contact with air for some time will contain peroxides. These should be removed by washing the ether, first with sodium bisulfite solution, then with sodium hydroxide solution, and finally with water. The ether is dried (twenty-four hours over calcium chloride, then twenty-four hours over phosphorus pentoxide) and distilled.

7. Heating to effect solution should be as brief as possible. The water bath should be at a temperature near the boiling point, and the flask should be immersed for only short periods of time. The flask should be shaken continuously during this process.

8. The product, m.p. 87–88°, is satisfactory for most pur-

poses. A single recrystallization from isopropyl ether gives a product having a melting point of 88-89°.

3. Methods of Preparation

α -Acetobromoglucose has been prepared by the action of acetyl bromide on anhydrous glucose;^{1, 2, 3, 4} by the action of hydrogen bromide in acetic acid upon β -pentaacetylglucose;^{5, 6, 7, 8} by the action of hydrogen bromide in acetic anhydride upon anhydrous glucose;^{9, 10} and by the action of hydrogen bromide in acetic anhydride upon starch or maltose.¹¹

¹ Koenigs and Knorr, Ber. **34**, 961 (1901).

² Colley, Ber. **34**, 3206 (1901).

³ Moll van Charante, Rec. trav. chim. **21**, 43 (1902).

⁴ Brauns, J. Am. Chem. Soc. **47**, 1280 (1925).

⁵ Fischer, Ber. **49**, 584 (1916).

⁶ Freudenberg, Noe, and Knopf, Ber. **60**, 241 (1927).

⁷ Fischer and Armstrong, Ber. **34**, 2892 (1901).

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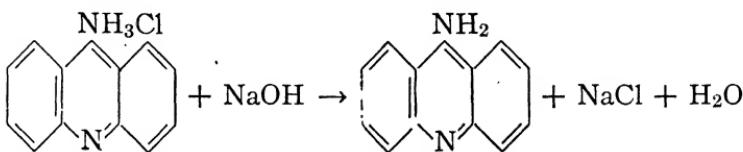
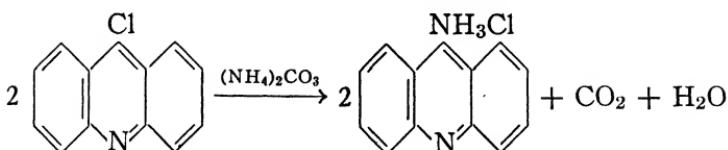
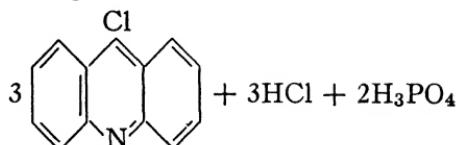
⁹ Dale, J. Am. Chem. Soc. **38**, 2187 (1916).

¹⁰ Levene and Raymond, J. Biol. Chem. **90**, 247 (1931).

¹¹ Bergmann and Beck, Ber. **54**, 1576 (1921).

9-AMINOACRIDINE

(Acridine, 5-amino-)



Submitted by ADRIEN ALBERT and BRUCE RITCHIE.
Checked by R. L. SHRINER and JOHN C. ROBINSON, Jr.

1. Procedure

IN a 500-cc. round-bottomed flask fitted with a water-cooled condenser, 50 g. (0.23 mole) of *N*-phenylanthranilic acid (Org. Syn. 19, 6) [or 46 g. acridone (Org. Syn. 19, 7)] is mixed with 160 cc. (270 g., 1.76 moles) of phosphorus oxychloride (Note 1). The mixture is slowly heated (about fifteen minutes) to 85–90° on a water bath. A vigorous reaction sets in, and the flask is removed at once from the hot bath. If the reaction becomes too violent, the flask is immersed in a beaker of cold water for a moment. After five to ten minutes, when the boiling subsides somewhat, the flask is immersed in an oil bath. The temperature of the bath is then raised to 135–140°, where it is maintained for two hours. The excess phosphorus oxychloride is removed by distillation from an oil bath at 140–150° under a vacuum of about 50 mm. The residue, after cooling, is poured into a well-stirred mixture of

200 cc. of concentrated ammonia solution, 500 g. of ice, and 200 cc. of chloroform. The flask is rinsed by shaking with a little chloroform-ammonia mixture (about 25–30 cc.). When no more undissolved solid remains (about half an hour is required), the chloroform layer is separated and the aqueous layer is extracted with an additional 40 cc. of chloroform. The united chloroform extracts are dried over 10 g. of calcium chloride and filtered, and the solvent is removed by distillation. The resultant greenish-gray powder is dried at 70° for twenty minutes (Notes 2 and 3). The yield of crude 9-chloroacridine is 50 g. (practically theoretical), m.p. 117–118° (Note 4).

In a 1-l. beaker are placed 50 g. (0.23 mole) of crude 9-chloroacridine and 250 g. (2.7 moles) of phenol (Note 5). The mixture is stirred mechanically while it is heated to 70° (internal temperature) in an oil bath. Stirring is continued, and 30 g. (0.38 mole) of powdered ammonium carbonate (Note 6) is added as rapidly as the vigorous effervescence permits. The internal temperature is quickly raised to 120° and maintained there while the mixture is stirred for forty-five minutes. The mixture is cooled to 30° and poured into 600 cc. of acetone in a beaker surrounded by ice. After about an hour, precipitation of 9-aminoacridine hydrochloride is complete and the product is filtered and washed free from phenol with 250 cc. of acetone (Note 7). The cake is extracted by boiling it with water three times, using successively 800, 200, and 100 cc., the last portion containing 2 cc. of concentrated hydrochloric acid. The hot solutions are filtered to remove the small amount of carbonaceous matter, and the filtrates are combined. Any precipitate is redissolved by heating, and then a solution of 60 g. of sodium hydroxide in 300 cc. of water is added. The mixture is cooled and filtered; the solid is washed with 300 cc. of cold water and dried at 120°. The yield is 34–38 g. (76–85 per cent of the theoretical amount based on phenylanthranilic acid or acridone) of bright yellow powder, m.p. 230°. This product is pure enough for most purposes, but the crude material may be purified by boiling 38 g. of it with 1.2 l. of acetone. The mixture is filtered by suction, and the filtrate is chilled in an ice-salt bath. The first crop weighs 26–27 g., and concentration of the

mother liquor to 500 cc. yields an additional 6-7 g. of crystals. Both crops melt at 232-233°, and the recovery is 32-34 g. (84-89 per cent) (Note 8).

2. Notes

1. The phosphorus oxychloride should be freshly distilled.
2. 9-Chloroacridine is readily hydrolyzed in neutral and acid solutions; hence it must not be exposed to the air after removal of the phosphorus oxychloride and before treatment with ammonia. If the drying is carried out at a higher temperature, loss results through sublimation. Care should be taken to keep 9-chloroacridine from entering the eyes, as it is distinctly irritating.
3. It was found convenient to dry the chloroacridine by pouring the concentrated chloroform extract directly into the 1-l. beaker to be used for the next step, and heating the oil bath to 70° for the required twenty minutes.
4. If pure 9-chloroacridine is desired, the crude product is dissolved in a little boiling alcohol, and 0.5 per cent ammonia is added until the solution becomes milky. About 0.5 g. of Norite is then added; the solution is quickly filtered and at once cooled in an ice bath. White crystals, melting at 119-120°, are obtained. The product keeps best in a desiccator over potassium carbonate. By warming 9-chloroacridine with various primary and secondary amines, many substituted 9-aminoacridines are readily obtained.
5. 9-Phenoxyacridine appears to be an intermediate in this reaction.
6. The ammonium carbonate should analyze for 30 per cent ammonia. Baker's analyzed ammonium carbonate (lump) is suitable.
7. The acetone and the phenol, recovered from the filtrate by simple distillation and by vacuum distillation, respectively, may be used again.
8. 9-Aminoacridine hydrochloride is one of the most highly fluorescent of substances. The 1:1000 aqueous solution is pale yellow with only a faint green fluorescence, but the 1:100,000 solution is colorless with an intense blue fluorescence.

9-Aminoacridine is a moderately strong base;¹ the dissociation constant is 3×10^{-5} (aniline = 5×10^{-10}).

3. Methods of Preparation

9-Chloroacridine has been prepared by heating thioacridone,¹ acridone,² or *N*-phenylanthranilic acid^{3, 4, 5} with phosphorus pentachloride, phosphorus oxychloride, or a mixture of the two phosphorus halides, with and without the addition of hydrocarbon solvents. The present method is essentially that of Magidson,³ but the troublesome filtration of the glutinous and easily hydrolyzed 9-chloroacridine has been avoided by the use of chloroform.

The method described for converting 9-chloroacridine to 9-aminoacridine was developed after experience with the methods given in the literature, namely: conversion of 9-chloroacridine, through 9,9-diphenoxycridan, to 9-phenoxyacridine, which is then heated with ammonium chloride;⁶ heating 9-chloro-, 9-ethoxy-, or 9-phenoxyacridine with ammonia and a copper compound under pressure,⁷ or with phenylhydrazine followed by acid reduction.⁸ 9-Aminoacridine has also been prepared by hydrolyzing 9-cyanoacridine (from acridine or 9-chloroacridine) to the corresponding acid amide, and subsequent degradation to the required amine;⁹ and by the decomposition of the acid azide.¹⁰ Some methods developed for preparing aminoethoxyacridines¹¹ are also of interest.

¹ Edinger, J. prakt. Chem. (2) **64**, 471 (1901).

² Graebe and Lagodin茨ki, Ann. **276**, 48 (1893).

³ Magidson, Ber. **66**, 866 (1933).

⁴ Derscherl, Ann. **504**, 300 (1933).

⁵ Drozdov, J. Gen. Chem. (U.S.S.R.) **4**, 117 (1934); [C. A. **28**, 5456 (1934)].

⁶ Drozdov, J. Gen. Chem. (U.S.S.R.) **5**, 1576, 1736 (1935); [C. A. **30**, 2195, 3432 (1936)].

⁷ Meister, Lucius, and Bruning, Ger. pat. 360,421 [Frdl. **14**, 800 (1921-1925); C. A. **18**, 1130 (1924)]; Ger. pat. 364,032 [Frdl. **14**, 802 (1921-1925); C. A. **18**, 1130 (1924)]; Ger. pat. 367,084 [Frdl. **14**, 803 (1921-1925); C. A. **18**, 1130 (1924)].

⁸ Meister, Lucius, and Bruning, Ger. pat. 364,031 [Frdl. **14**, 801 (1921-1925); C. A. **18**, 1131 (1924)].

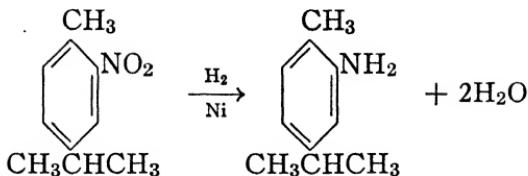
⁹ Lehrnstedt, Ber. **64**, 1232 (1931).

¹⁰ Meister, Lucius, and Bruning, Ger. pat. 364,035-6 [Frdl. **14**, 805-806 (1921-1925); C. A. **18**, 1131 (1924)].

¹¹ Meister, Lucius, and Bruning, Ger. pat. 393,411 [Frdl. **14**, 807 (1921-1925)]; Ger. pat. 395,683 [Frdl. **14**, 812 (1921-1925)].

2-AMINO-*p*-CYMENE

(Carvacrylamine)



Submitted by C. F. H. ALLEN and JAMES VAN ALLAN.
Checked by HOMER ADKINS.

1. Procedure

A MIXTURE of 179 g. (167 cc., 1 mole) of 2-nitro-*p*-cymene (Org. Syn. 21, 96), 300 cc. of absolute alcohol, and 3–5 g. of Raney nickel (Org. Syn. 21, 15) is placed in the steel reaction vessel of a high-pressure hydrogenation apparatus (Org. Syn. 19, 48–51).¹ The bomb is then closed, and hydrogen is admitted until the pressure, at 25°, is about 1000 lb. While the bomb is shaken, the temperature is rapidly raised to 80–90°, and then the heater is shut off (Note 1). Owing to the strong exothermic reaction, the temperature continues to rise, reaching about 120°, while the pressure drops rapidly. The pressure in the reaction vessel is maintained at 700–1500 lb., by the introduction of hydrogen from a tank, until the rapid reaction is over (fifteen minutes). The reaction mixture is kept at 100–120° for thirty minutes after there is no further drop in the pressure of hydrogen. After the bomb has cooled, the hydrogen is slowly released and the catalyst is separated from the reaction mixture by centrifuging, or by filtration through a sintered glass or Büchner funnel (Note 2). The alcohol and water are removed by distillation, and the product is fractionated in a suitable apparatus (Notes 3, 4, 5, 6, 7).

¹ American Instrument Company, Silver Springs, Maryland, or Parr Instrument Company, Moline, Illinois.

The amine distils at 239–240°/740 mm., 242° (corr.)/760 mm., 110°/10 mm., or 92–94°/2 mm. In the first distillation the portion boiling below 225°/740 mm. (or below 100°/9 mm.) is discarded. The yield is 130–135 g. (87–90 per cent of the theoretical amount).

2. Notes

1. The hydrogenation of nitro compounds liberates so much heat, and the reaction may proceed so rapidly, that precautions must be taken against excessive reaction temperatures. Temperatures of 150–200° may bring about the formation of secondary amines, and at higher temperatures decomposition reactions may occur with explosive violence. These dangers may be avoided by the use of small amounts of catalyst and by having an insufficient amount of hydrogen in the reaction vessel at the beginning of the reaction. After sufficient hydrogen for the hydrogenation of half of the nitro compound has been taken up there need be no fear that the reaction will proceed too rapidly. It is always desirable, however, to complete the hydrogenation as rapidly as possible while avoiding temperatures above about 120°. The use of alcohol as a solvent prevents the separation of a water layer, which would cover most of the catalyst and thus give rise to a slow and perhaps incomplete hydrogenation.

2. If the sample of nitrocymene is impure, or if the catalyst is of poor quality, the hydrogenation may not proceed to completion and a solution of the product in hydrochloric acid will be turbid. In this event, the mixture of products (after separation of the spent catalyst) may again be submitted to hydrogenation. An alternative procedure involves removal of the non-basic material by steam distillation of a mixture of the product with 350 cc. of water and 90 cc. of concentrated hydrochloric acid. The amine is then liberated from its salt by the addition of 45 g. of sodium hydroxide and is extracted with 500 cc. of ether. The ether layer may be siphoned from the water layer. The ether is removed by distillation, and the residue is fractionated as described in the procedure. For steam distillations, the submitters employ the adapter shown in Fig. 1. With this adapter the

apparatus is much more compact than in the usual arrangement, for the receiver may serve as a partial condenser, as in distillation under reduced pressure.

3. The apparatus may consist of a modified Claisen flask, or of an ordinary flask connected to a Vigreux, Widmer, modified Widmer, or other column. The checker used a modified Widmer column (Org. Syn. 20, 53), and a distillation at 9 mm. pressure. The submitters conducted the distillation at atmospheric pres-

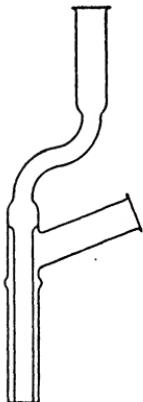


FIG. 1

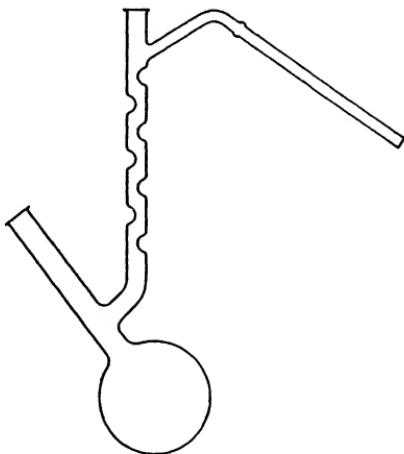


FIG. 2

sure, in the type of flask shown in Fig. 2. This type of flask, as well as the adapter described in Note 2, have been used in the laboratories of the Eastman Kodak Company for some time. In comparison with the standard Claisen flask, this flask has several advantages. It has a longer column; liquids seldom bump over, consequently more material may be handled in a flask of given size; and material which has come into contact with the rubber stopper cannot contaminate the distillate. No dimensions are given for the flask, or for the adapter described in Note 2 above; these pieces may be constructed in various sizes to suit individual needs.

4. Nitrocymene usually contains about 8 per cent of *p*-nitrotoluene. The complete separation of the resulting *p*-toluidine

from the 2-amino-*p*-cymene requires a rather careful fractionation.

5. If air comes in contact with the hot amine vapor, the product will be colored. However, a product distilled at 9 mm. with a capillary ebullition tube was only faintly yellow.

6. The reduction may also be carried out at lower pressures in the usual laboratory apparatus (Org. Syn. Coll. Vol. 1, 1st Ed. (1932), p. 53; 2nd Ed. (1941), p. 63). A mixture of 50 g. of nitrocymene, 200 cc. of 95 per cent alcohol, and 5 g. of Raney nickel is reduced at 85–90°, at an initial pressure of 55–60 lb.; the time required is six hours. The product is processed as described above. The yield is 33–36 g. (80–85 per cent of the theoretical amount).

7. Nitrocymene may also be reduced by the use of iron powder, essentially as described under 2,4-diaminotoluene (Org. Syn. 11, 32) (Kenneth A. Kobe, private communication).²

3. Methods of Preparation

Because of the accessibility of *p*-cymene, reduction of the nitro derivative constitutes the only practical method for preparation of 2-aminocymene. Tin,^{3, 4, 5} and iron,^{6, 7} together with hydrochloric acid, have been used for this purpose. A patent⁶ mentions the use of hydrogen in the presence of a nickel catalyst.

² Doumani and Kobe, J. Am. Chem. Soc. **62**, 563 (1940).

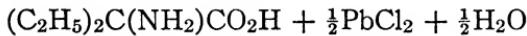
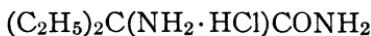
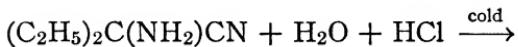
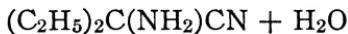
³ Soderbaum and Widman, Ber. **21**, 2127 (1888).

⁴ Wheeler and Smithey, J. Am. Chem. Soc. **43**, 2613 (1921).

⁵ Demonbreun and Kremers, J. Am. Pharm. Assoc. **12**, 296 (1923). [C. A. **17**, 3906 (1923)].

⁶ Andrews, U. S. pat. 1,314,920 [C. A. **13**, 2765 (1919)].

⁷ Doumani and Kobe, Ind. Eng. Chem. **31**, 264 (1939).

α -AMINODIETHYLACETIC ACID(Butyric Acid, α -amino- α -ethyl-)

Submitted by ROBERT E. STEIGER.

Checked by W. E. BACHMANN and YUN-TSUNG CHAO.

1. Procedure

A SOLUTION of 50 g. (1 mole) of sodium cyanide (98 per cent purity) in 100 cc. of water is placed in a 2-l. round-bottomed flask (Note 1) fitted with a ground-glass stopper. A solution of 58.9 g. (1.1 moles) of ammonium chloride in 140 cc. of lukewarm water is added, followed by 67 cc. (1 mole) of concentrated ammonium hydroxide (sp. gr. 0.9). This mixture is stirred mechanically and is cooled by a stream of water while a solution of 86.1 g. (1 mole) of diethyl ketone in 160 cc. of methyl alcohol (Note 2) is added. The flask is then stoppered (Note 3) and half immersed for five hours in a water bath, the temperature of which is kept at 55–60°. The reaction mixture is then cooled in an ice bath and poured (with precautions, i.e., under a properly ventilated hood) into 800 cc. of concentrated hydrochloric acid (sp. gr. 1.18) contained in a 5-l. round-bottomed flask which is surrounded up to the neck by ice and water. The reaction flask is rinsed with two

25-cc. portions of water. The mixture is now saturated at 0-5° with hydrogen chloride gas. After standing overnight under a hood, the mixture is refluxed for two and one-half hours (Note 4).

The solution is evaporated to dryness under reduced pressure on a water bath. In order to remove as much hydrochloric acid as possible, the temperature of the bath is raised to 100° toward the end of the distillation. The residue of amino acid hydrochloride and inorganic salts is suspended in 500 cc. of absolute ethyl alcohol. The suspension is boiled on a steam bath for a short time, then cooled to room temperature and filtered on a Büchner funnel. The residue of inorganic salts is washed with 500 cc. of absolute ethyl alcohol. To the combined filtrates is added 400 cc. of ethyl ether (u. s. p. quality) in order to precipitate inorganic material. After several hours the mixture is filtered, and the residue is washed with a 5:2 mixture of absolute ethyl alcohol and ether. The filtrate is transferred to a 5-l. round-bottomed flask, about 200 cc. of water is added, and the liquids are removed by distillation under reduced pressure. The nearly dry residue is dissolved in 2 l. of water, and the solution is treated with an excess of freshly prepared lead hydroxide (Note 5). The suspension is diluted with water to a volume of about 3.5 l. and is then concentrated under reduced pressure, at as low a temperature as possible, to a volume of about 2 l. The suspension is then filtered with suction (Note 6), and the residue of lead salts is washed thoroughly with water. The cloudy filtrate, which still contains some free ammonia, is concentrated by distillation under reduced pressure to a volume of about 300-400 cc. The mixture is filtered, the filtrate is saturated with hydrogen sulfide gas, and the precipitate of lead sulfide is removed by filtration with suction (Note 6). The solution is now concentrated by distillation under reduced pressure on a water bath, and 1 l. of 95 per cent ethyl alcohol is added to the nearly dry residue of the amino acid. The suspension is boiled under a reflux condenser until nearly all the amino acid is dissolved, and the mixture is then allowed to cool to room temperature. The amino acid, which separates in the form of fine needles, is collected on a Büchner funnel and washed with a little 95 per cent ethyl alcohol. A second crop of

crystals is obtained by evaporating the combined filtrates to dryness, dissolving the residue in the minimum amount of hot water, and treating the solution with 95 per cent ethyl alcohol. The amino acid is dried in the air and then in a vacuum desiccator over phosphorus pentoxide. The total yield of product is 58.8–65 g. (39–43 per cent of the theoretical amount, assuming that the product contains exactly one molecule of water of crystallization) (Note 7).

2. Notes

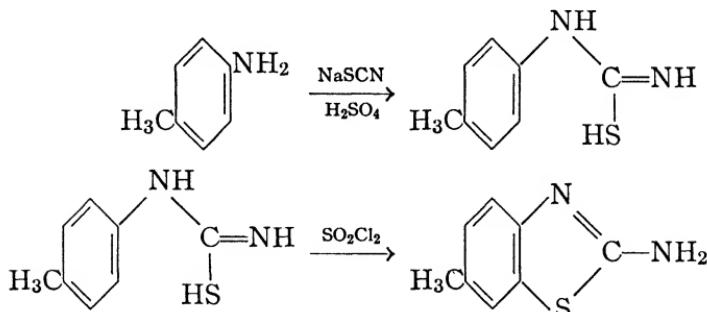
1. The checkers used a 1-l. Erlenmeyer flask fitted with a ground-glass stopper.
2. The methyl alcohol must be free from acetone since this ketone would give rise to α -aminoisobutyric acid.
3. The ground-glass stopper should be lubricated slightly with stopcock grease. It must be secured firmly by means of adhesive tape, as some pressure develops when the flask is heated.
4. The hydrolysis must be carried out under a hood. The top of the reflux condenser should be connected with the ventilation pipe by means of a piece of glass tubing. The methyl alcohol contained in the reaction mixture escapes in the form of methyl chloride, along with some hydrogen chloride.
5. The lead hydroxide is prepared by adding 1.5 l. of a 2 N solution of sodium hydroxide (3 moles) through a dropping funnel to a continuously stirred solution of 569 g. (1.5 moles) of lead acetate, $(\text{CH}_3\text{CO}_2)_2\text{Pb} \cdot 3\text{H}_2\text{O}$, in 1.35 l. of water. The precipitate is collected on a 13-cm. Büchner funnel and washed well with water in order to remove water-soluble impurities. The paste of lead hydroxide is transferred to the solution that is to be freed of chloride ions.
6. A Büchner funnel of adequate size is fitted with two pieces of hardened filter paper covered with a thin layer of moistened Norite.
7. The checkers obtained 65 g. of pure amino acid in the first crop; the second crop of 5 g. contained chloride ion. When heated in an open tube, the pure product sublimed at 255° without melting.

3. Methods of Preparation

α -Aminodiethylacetic acid has been prepared from α -bromo-diethylacetic acid and ammonia;¹ and by hydrolysis of α -amino-diethylacetonitrile with hydrochloric acid.^{1, 2, 3, 4} The required nitrile was obtained by heating diethyl ketone cyanohydrin with one equivalent of ethyl alcoholic ammonia;² by heating diethyl ketone with an alcoholic solution of ammonium cyanide;³ and by heating diethyl ketone with a solution of potassium cyanide and ammonium chloride.^{1, 4}

2-AMINO-6-METHYLBENZOTHIAZOLE

(Benzothiazole, 1-amino-5-methyl-)



Submitted by C. F. H. ALLEN and JAMES VAN ALLAN.
Checked by W. E. BACHMANN and N. W. MACNAUGHTON.

1. Procedure

A SOLUTION of 107 g. (1 mole) of *p*-toluidine (Note 1) in 700 cc. of chlorobenzene is prepared in a 3-l. three-necked, round-bottomed flask fitted with a stirrer, reflux condenser, thermometer, and dropping funnel. Over a period of five minutes, 54 g. (29.3 cc.,

¹ Rosenmund, Ber. **42**, 4472 (1909).

² Tiemann and Friedländer, Ber. **14**, 1973 (1881).

³ Gulewitsch and Wasmus, Ber. **39**, 1191 (1906).

⁴ Freytag, Ber. **48**, 649 (1915).

0.55 mole) of concentrated sulfuric acid is added dropwise. To the finely divided suspension of *p*-toluidine sulfate is added 90 g. (1.1 moles) of sodium thiocyanate, and the mixture is heated for three hours at 100° (inside temperature) in an oil bath (Note 2). The solution, which now contains the thiourea, is cooled to 30°, and 180 g. (108 cc., 1.34 moles) of sulfuryl chloride is added over a period of fifteen minutes, with care that the temperature does not exceed 50°. The mixture is kept at 50° for two hours (no further evolution of hydrogen chloride), after which the chlorobenzene is removed by filtration (Note 3).

The solid residue is then dissolved in 1 l. of hot water, and the remainder of the solvent is removed by a current of steam (Note 4). The solution is filtered from a little solid and is then made alkaline to litmus by the addition of 200 cc. of concentrated ammonium hydroxide (sp. gr. 0.90). The precipitated amino-methylbenzothiazole is filtered and washed with 200 cc. of water. The solid, which melts over the range 123–128°, is dissolved in 300 cc. of hot alcohol (Note 5), 10 g. of Norite is added, and the hot suspension is filtered. The filtrate is diluted with 500 cc. of hot water, and the mixture is vigorously stirred and quickly chilled. After half an hour, the pale yellow granular product is filtered and washed with 150 cc. of 30 per cent alcohol. After drying to constant weight, the product weighs 100–105 g. and melts at 135–136°, with preliminary shrinking at 130–131° (Note 6). On addition of 200 cc. of water to the filtrate, a further 5–8 g. of product is recovered, making the total yield 105–110 g. (64–67 per cent of the theoretical amount).

2. Notes

1. All the chemicals used were from the Eastman Kodak Company. The checkers used the Practical grade of *p*-toluidine, which was distilled just before use.
2. The *p*-tolylthiourea may be isolated at this point, if desired, by filtering and washing the solid residue with ether. The dried solid (172 g.) is a mixture of the urea and sodium sulfate. It is extracted with 250 cc. of warm (50–60°) water; the residual urea,

m.p. 188–189°, is completely soluble in alcohol. The yield is 139 g. (84 per cent of the theoretical amount).

3. The recovery is about 600 cc.; it may be used again without purification.

4. Treatment of the solution with Norite at this point does not give a product of any better quality.

5. If less alcohol is used, crystallization takes place during filtration.

6. The literature gives melting points ranging from 128° to 142°, the higher value being for aminomethylbenzothiazole prepared via the hydrochloride (m.p. 250–253°). The submitters report that the product obtained above is unchanged in melting point after regeneration from the hydrochloride. By this treatment, however, the color is removed.

3. Methods of Preparation

2-Amino-6-methylbenzothiazole has been prepared by the action of cupric thiocyanate,^{1, 2, 3} or of chloramine and ammonium thiocyanate,⁴ on *p*-toluidine; by the action of chlorine on di-*p*-tolylthiourea;⁵ or of bromine on acetyl-di-*p*-tolylthiourea;⁶ by treatment of *p*-tolylthiourea with halogens⁷ or acid halides.^{8, 9, 10, 11, 12} 2-Aminobenzothiazole has been prepared in

¹ Kaufmann, Oehring, and Clauberg, Arch. Pharm. **266**, 197 (1928). [C. A. **22** 2166 (1928)].

² Kaufmann and Küchler, Ber. **67**, 946 (1934).

³ Kaufmann, Ger. pat. 579,818 [C. A. **28**, 1053 (1934)].

⁴ Likhoshsterstov and Petrov, J. Gen. Chem. (U.S.S.R.) **3**, 759 (1933) [C. A. **28**, 2690 (1934)].

⁵ I. G. Farbenind. A-G., Fr. pat. 688,867 [C. A. **25**, 968 (1931)].

⁶ Hunter and Jones, J. Chem. Soc. **1930**, 2197.

⁷ Hunter, J. Chem. Soc. **1926**, 1399.

⁸ Herz and Schubert, U. S. pat. 2,003,444 [C. A. **29**, 4774 (1935)].

⁹ I. G. Farbenind. A-G., Brit. pat. 345,735 [C. A. **26**, 1944 (1932)].

¹⁰ E. I. du Pont de Nemours and Company, Fr. pat. 727,410 [C. A. **26**, 5103 (1932)].

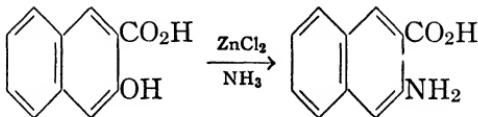
¹¹ Herz and Schubert, Ger. pat. 537,105 [Frdl. **17**, 615 (1932); C. A. **26**, 1000 (1932)].

¹² Schubert and Schütz, Ger. pat. 604,639 [Frdl. **21**, 227 (1934); C. A. **29**, 819 (1935)].

excellent yield by the action of hydroxylamine upon benzothiazole.¹³

3-AMINO-2-NAPHTHOIC ACID

(2-Naphthoic Acid, 3-amino-)



Submitted by C. F. H. ALLEN and ALAN BELL.

Checked by NATHAN L. DRAKE, E. W. REEVE, and J. VAN HOOK.

1. Procedure

AN autoclave (Note 1) is charged *successively* with 600 cc. (9.5 moles) of approximately 28 per cent aqueous ammonia, 78 g of zinc chloride (0.57 mole) (Notes 2 and 3), and 167 g. of 3-hydroxy-2-naphthoic acid (0.89 mole) (Note 4). The autoclave is closed, and then, with continuous stirring or shaking (Note 5), it is gradually heated, so that, at the end of three hours, the temperature is 195°. This temperature is maintained for thirty-six hours; the pressure is about 400 lb. (Note 6). The autoclave is allowed to cool to room temperature, with continuous stirring or shaking. The cover is removed, the solid is scraped off the walls, and the reaction mixture is transferred to a 5-l. flask. The autoclave is rinsed with two 700-cc. portions of water, which are added to the reaction mixture.

To the reaction mixture is added 660 g. of concentrated hydrochloric acid (sp. gr. 1.18), and the suspension is boiled for half an hour. It is then filtered, while hot, through a Büchner funnel. The residual cake is boiled again, for the same length of time, with a mixture of 500 cc. of water and 30 cc. of concentrated hydrochloric acid, and then filtered as before.

The combined filtrates, on cooling, deposit the hydrochloride of the aminonaphthoic acid; this is filtered with suction and is

¹³ Skraup, Ann. 419, 65 (1919).

pressed as dry as possible. To obtain a second crop of the hydrochloride, the filtrate is heated to 85°, 500 g. of salt is added, and the solution is cooled.

The combined moist filter cakes are placed in a 5-l. flask with 1.3 l. of water, and, with stirring, sufficient 40 per cent sodium hydroxide solution is added to make the solution just alkaline to Clayton yellow paper (Note 7); about 110 cc. is required. The mixture is heated to 85° and is filtered to remove a small amount of insoluble material. The filtrate is then made acid to Congo red by addition of concentrated hydrochloric acid (about 100 cc. of acid is required). The mixture is stirred for fifteen minutes, and then enough 10 per cent sodium acetate solution is added so that Congo red paper is no longer turned blue; the amount needed depends on the acidity; usually about 15 cc. is sufficient.

The hot mixture is filtered; the aminonaphthoic acid is washed on the Büchner funnel with 400 cc. of hot water and is pressed as dry as possible. The product is dried at 50° to constant weight (twenty-four to thirty-six hours). 3-Amino-2-naphthoic acid is a yellow, powdery substance, which melts at 214–215° (Note 8); the yield is 110–115 g. (66–70 per cent of the theoretical amount) (Note 6). The quantities of starting materials are limited only by the size of the autoclave available; the yield (per cent) in large runs is the same as that obtained above.

2. Notes

1. An autoclave fitted for stirring or shaking is essential. An example of the former is the one furnished by the Will Corporation, catalog No. 1735. This is large enough so that three times the amounts specified may be handled. A hydrogenation autoclave of the type supplied by the American Instrument Company, catalog No. 406-21, having a capacity of about 1.4 l., may also be used. This type of autoclave is not fitted with a stirrer but is shaken by means of a "Bomb Shaker" in which the autoclave is placed. In using the hydrogenation autoclave, the long hydrogen inlet tube, which extends half way into the chamber of the autoclave, is unscrewed and removed. The inlet for hydro-

gen, on the outside of the autoclave, is closed by means of a solid steel rod, the end of which is finished and held in place in the same manner as the ordinary steel pressure tubing.

After making a run, the hydrogenation autoclave is poisoned for hydrogenations. It may be cleaned by filling it with 5 per cent hydrochloric acid and rubbing the inside walls with a cloth or brush. It should then be washed with water and dried; any solid matter adhering to the walls is removed by rubbing with emery paper. Care must be taken not to scratch either the copper gasket or the groove into which the gasket fits. All parts of the hydrogenation autoclave, including the head, must be thoroughly cleaned. Traces of the reaction product will cause pitting in a few hours if they are allowed to remain in contact with the steel while the bomb is exposed to the air.

After the hydrogenation autoclave is cleaned it is best to carry out one or two ester hydrogenolyses with copper chromite in order to remove the last traces of "poison." The bomb may then be used for hydrogenations.

2. The zinc chloride should not contain appreciable amounts of the oxychloride.

3. Since zinc chloride and aqueous ammonia react with evolution of heat, the solid must be added gradually and with hand stirring. It is best to carry out this operation under a hood.

4. A technical grade of 3-hydroxy-2-naphthoic acid, m.p. 211-214°, was used.

5. Continued stirring or shaking is required throughout, i.e., from the time heating is begun until the reaction product has again attained room temperature. With a hydrogenation autoclave there will be no trouble due to leaks, but with the stirrer type of autoclave the packing around the stirrer shaft may leak. In this event the pressure will fall and a longer period of time will be required. If a large quantity of ammonia escapes, the yield will be diminished, but the run should be finished and the unused hydroxynaphthoic acid should be recovered and used in another run.

6. In a run in which the gaskets leaked, the pressure never exceeded 200 lb. In this run, the (stirrer-type) autoclave was

operated for five days; the yield was 67 per cent of the theoretical amount.

7. Clayton yellow paper (thiazole paper) is paper impregnated with the dye formed by coupling diazotized primuline sulfonic acid with primuline sulfonic acid. The color change occurs at *pH* 11-12. If this paper is not available, a little less than the estimated amount of alkali should be used. The mixture is warmed to 85°, and a small test portion is removed and warmed with more alkali. If any appreciable amount of the insoluble matter dissolves, more alkali is needed.

8. This product is pure enough for most purposes. It can be recrystallized from alcohol (10 g. dissolves in 100 cc. of hot alcohol); the recovery is 78 per cent (7.8 g.), and the purified product melts at 216-217°.

3. Methods of Preparation

3-Amino-2-naphthoic acid has been prepared by heating 3-hydroxy-2-naphthoic acid with ammonia under pressure, in the presence of catalysts. These catalysts include zinc (or calcium) chloride;^{1, 2, 3, 4} alone or with addition of aluminum chloride.⁵ Zinc oxide or carbonate and ammonium chloride,^{6, 7, 8} or ferrous ammonium salts,^{9, 10} have also been used. When sodium hydroxynaphthoate is heated with 35 per cent ammonia at 260-280°, the

¹ Soc. anon. pour l'ind. chim. à Bâle, Brit. pat. 250,598 [Frdl. 16, 487 (1927-1929); C. A. 21, 1127 (1927)].

² Tobler, U. S. pat. 1,629,894 [Frdl. 16, 487 (1927-1929); C. A. 21, 2273 (1927)].

³ I. G. Farbenind. A-G., Brit. pat. 284,998 [Frdl. 16, 484 (1927-1929); C. A. 22, 4540 (1928)].

⁴ Henle and Lanz, U. S. pat. 1,871,990 [C. A. 26, 5971 (1932)].

⁵ Fierz and Tobler, Helv. Chim. Acta 5, 558 (1922).

⁶ Dutta, Ber. 67, 1321 (1934).

⁷ I. G. Farbenind. A-G., Brit. pat. 330,941 [Frdl. 16, 2999 (1927-1929); C. A. 24, 5768 (1930)].

⁸ Schweitzer, U. S. pat. 1,806,714 [Frdl. 16, 2998 (1927-1929); C. A. 25, 4012 (1931)].

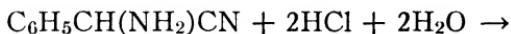
⁹ I. G. Farbenind. A-G., Brit. pat. 282,450 [Frdl. 16, 487 (1927-1929); C. A. 22, 3669 (1928)].

¹⁰ Hotz and Lanz, U. S. pat. 1,690,785 [Frdl. 16, 487 (1927-1929); C. A. 23, 397 (1929)].

product is contaminated with considerable amounts of β -naphthol and β -naphthylamine.¹¹

dL- α -AMINOPHENYLACETIC ACID

(*dl*-Phenylglycine; α -Toluic Acid, α -amino, *dl*-)



Submitted by ROBERT E. STEIGER.

Checked by R. L. SHRINER, S. P. ROWLAND, and C. H. TILFORD.

1. Procedure

To a solution of 100 g. (2.0 moles) of 98 per cent sodium cyanide in 400 cc. of water, contained in a 3-l. round-bottomed flask fitted with a Hershberg stirrer (Org. Syn. 17, 31), is added 118 g. (2.2 moles) of ammonium chloride. The mixture is stirred at room temperature under a properly ventilated hood. When the ammonium chloride has dissolved, a solution of 212 g. (2.0 moles) of benzaldehyde in 400 cc. methyl alcohol is added in one portion. The reaction begins rapidly, the temperature rising to about 45°. Stirring is continued for two hours. The heterogeneous mixture, after dilution with 1 l. of water, is extracted with 1 l. of benzene, and the aqueous layer is discarded. The benzene layer is washed with three 50-cc. portions of water, and the aminonitrile is extracted, in the form of its hydrochloride, by shaking the benzene solution with 6 *N* hydrochloric acid, first with one 600-cc. portion and then with two 300-cc. portions.

¹¹ Möhlau, Ber. 28, 3096 (1895).

The combined acid extracts are placed in a 3-l. round-bottomed flask and refluxed for two hours (Note 1). The hydrolysate is diluted with water to bring its volume to about 2 l. and is then subjected to distillation under reduced pressure (20–30 mm.) to remove all benzaldehyde and other volatile substances (Note 2). To remove some resinous matter deposited in the course of the hydrolysis, the mixture is treated with 10 g. of Norite and filtered through a Büchner funnel. The yellow filtrate is transferred to a 3-l. beaker. It is stirred by hand with a thick glass rod while ammonium hydroxide (sp. gr. 0.90) is added through a dropping funnel until the liquid is faintly alkaline to litmus (Note 3). The mixture becomes quite hot and acquires a strong odor of benzaldehyde. The amino acid separates in the form of yellow crystals. The mixture is cooled to room temperature, and the crystals are collected on a 15-cm. Büchner funnel. After washing with about 1 l. of water in small portions to remove the ammonium chloride, the solid is washed successively with 150 cc. of ethyl ether, three 50-cc. portions of hot 95 per cent ethyl alcohol, and finally with about 500 cc. of water. The crystals, when dried by suction, weigh 220 to 240 g. (Note 4). Drying is completed in a vacuum desiccator over phosphorus pentoxide. The yield of crude amino acid is 102–116 g. (34–39 per cent of the theoretical amount).

For purification, the product is dissolved in 800 cc. of 1 *N* sodium hydroxide, 500 cc. of ethyl alcohol is added, and the solution is filtered. The filtrate is transferred to a 2-l. beaker and is heated to the boiling point. Then 160 cc. of 5 *N* hydrochloric acid is slowly added, through a dropping funnel, while stirring by hand. The mixture is cooled to room temperature and is filtered with suction. The product is washed with 100 cc. of ethyl alcohol, then with 200 cc. of water, and is dried in a vacuum desiccator over phosphorus pentoxide. The nearly white, lustrous platelets have no definite melting point (Note 5). The yield of pure amino acid is 98–112 g. (33–37 per cent of the theoretical amount) (Note 6).

2. Notes

1. The hydrolysis of the aminonitrile should be carried out under a hood, since some hydrocyanic acid is liberated.

2. During this process, the volume of the solution must be maintained at about 2 l. by the frequent addition of water through a dropping funnel. Otherwise the hydrochloride of *dl*-phenylglycine, which is sparingly soluble in concentrated hydrochloric acid, may separate.

3. From 375 to 425 cc. of ammonium hydroxide of sp. gr. 0.90 is required.

4. This crude product is hydrated.

5. The decomposition range was about 270–280° with sintering at 258°. A new sample, when placed in the melting-point bath at 280–300°, sintered, and then decomposed at 300–302°.

6. Increasing the quantities of cyanide and ammonium chloride to three moles does not markedly improve the yields.

3. Methods of Preparation

dl-Phenylglycine has been prepared by heating α -bromo-phenylacetic acid with three times its weight of ammonium hydroxide (sp. gr. 0.90) to 100–110°;¹ by hydrolysis of α -amino-phenylacetonitrile with dilute hydrochloric acid;^{2, 3} and by reduction of benzoylformic acid phenylhydrazone with sodium amalgam in dilute sodium hydroxide.⁴ The method described above is, with some modifications and additions, the procedure used by Marvel and Noyes.^{3, 5}

¹ Stöckenius, Ber. 11, 2002 (1878).

² Tiemann, Ber. 13, 383 (1880); Ulrich, Ber. 37, 1688 (1904); Zelinsky and Stadnikoff, Ber. 39, 1725 (1906); 41, 2062 (1908); Ingersoll and Adams, J. Am. Chem. Soc. 44, 2933 (1922).

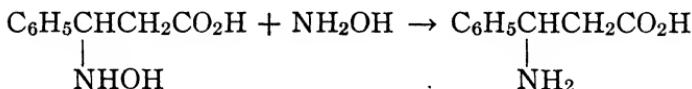
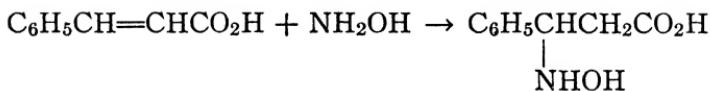
³ Marvel and Noyes, J. Am. Chem. Soc. 42, 2264 (1920).

⁴ Elbers, Ann. 227, 343 (1885).

⁵ Dr. D. Stetten, Jr. (private communication), recently found that when the synthesis is carried out according to Zelinsky and Stadnikoff, Ber. 41, 2062 (1908), and the amino acid is isolated in the fashion described above, the yield is not appreciably higher than the one recorded here.

dl- β -AMINO- β -PHENYLPROPIONIC ACID

(Hydrocinnamic Acid, β -amino-*dl*-)



Submitted by ROBERT E. STEIGER.

Checked by W. E. BACHMANN and YUN-TSUNG CHAO.

1. Procedure

A hot solution of sodium ethoxide is prepared, in a 3-l. round-bottomed flask, from 46 g. (2 gram atoms) of sodium and 1.6 l. of absolute ethyl alcohol. With shaking, a solution of 139 g. (2 moles) of hydroxylamine hydrochloride in 100 cc. of hot water is added. The resulting suspension is cooled quickly by placing the flask in an ice-water mixture and is then filtered with suction through a Büchner funnel. The residue of sodium chloride is washed with small portions (total 200 cc.) of absolute ethyl alcohol. The filtrate is returned to the 3-l. flask, and to it is added 148 g. (1 mole) of cinnamic acid, whereupon a voluminous precipitate forms. The mixture is refluxed on a steam bath for nine hours (Note 1). The amino acid begins to separate after five to six hours; the suspended solid causes the mixture to bump (Note 2). The suspension is allowed to remain overnight at room temperature, and the crystals are then collected on a Büchner funnel (Note 3). The product is washed with 300 cc. of absolute ethyl alcohol, then with some ice-cold water to remove all the sodium chloride, and finally with 300 cc. of absolute ethyl alcohol, always in small portions. The colorless crystals of amino acid are dried in a vacuum desiccator over flake sodium hydroxide. The yield is 56 g. (34 per cent of the theoretical amount).

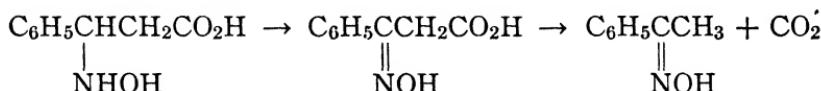
If a purer product is desired, the amino acid is dissolved in 16 times its weight of boiling water, and to the solution is added absolute ethyl alcohol (46 cc. per g. of acid). The solution is stirred mechanically while it is cooled in an ice-water mixture. After three hours, the snow-white crystals are collected on a Büchner funnel and are washed with 300 cc. of 95 per cent ethyl alcohol, in small portions, and dried as before. The recovery of amino acid, melting at 221° with decomposition (Note 4), is 81 per cent.

2. Notes

1. The solution becomes clear when the boiling point is reached. It is important that the mixture be boiled for the specified time in order to ensure complete conversion of the hydroxylamino acid into the amino acid. The solubilities of these two acids are nearly the same.

2. It may happen that the hot solution remains supersaturated, and crystallization does not take place, until the solution is cooled. The checkers obtained a poor yield when this occurred. They, therefore, seeded other runs during the boiling process in order to bring about crystallization. Posner¹ had to concentrate the solution to about half its volume in order to bring about crystallization.

3. The mother liquors from the crystallization appear to be free of amino acid if the yield mentioned is obtained. Among other products they contain at least 19 g. of acetophenoneoxime (14 per cent), which is formed by the secondary reaction:



The acetophenoneoxime may be isolated by evaporating the mother liquors almost to dryness, adding water repeatedly to remove the alcohol, and then treating the oily residue with 1*N* sodium carbonate solution.

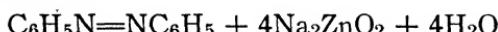
¹ Posner, Ber. **38**, 2320 (1905); Ann. **389**, 120 (1912). See also Fischer, Scheibler, and Grob, Ber. **43**, 2024 (1910).

4. The melting point varies considerably with the rate and duration of heating. Values ranging from 215° to 231° have been reported in the literature. The product obtained appears to be perfectly stable and shows no tendency to assume the pink coloration reported by Posner.¹

3. Methods of Preparation

The procedure described is that given by Posner,¹ with some modifications and additions. The amino acid has also been prepared by boiling the oxime hydrate of β -hydroxylaminohydrocinnamohydroxamic acid with water,² and by decarboxylation of β -amino- β -phenylethane- α , α -dicarboxylic acid.³

AZOBENZENE



Submitted by H. E. BIGELOW and D. B. ROBINSON.
Checked by W. E. BACHMANN and W. S. STRUVE.

1. Procedure

A 5-l. three-necked round-bottomed flask, fitted with a mercury-sealed stirrer and a reflux condenser, is placed on a steam cone. In the flask are placed 250 g. (208 cc., 2 moles) of nitrobenzene, 2.5 l. of methanol, and a solution of 325 g. (8.1 moles) of sodium hydroxide (Note 1) in 750 cc. of distilled water. To the mixture is added 265 g. (4.1 moles) of zinc dust (Note 2), the stirrer is started, and the mixture is refluxed for ten hours (Note 3). The mixture is filtered while hot, and the precipitate of sodium zincate is washed on the filter with a little warm

¹ Posner, Ber. 40, 227 (1904).

² Rodionow and Malewinskaja, Ber. 59, 2956 (1926); Rodionow, J. Am. Chem. Soc. 51, 851 (1929); Evans and Johnson, ibid. 52, 5001 (1930); Johnson and Livak, ibid. 58, 301 (1936).

methanol. All the methanol is distilled from the filtrate, the residue is chilled, and the crystalline azobenzene is filtered.

In order to remove zinc salts from the crude azobenzene, the latter is added to 500 cc. of 2 per cent hydrochloric acid, the mixture is warmed to about 70° in order to melt the azobenzene and is stirred rapidly for about five minutes. Stirring is continued while the mixture is chilled to solidify the azobenzene. The product is filtered, washed well with water, and recrystallized from a mixture of 720 cc. of 95 per cent alcohol and 60 cc. of water. The yield of azobenzene melting at 66–67.5° is 156–160 g. (84–86 per cent of the theoretical amount).

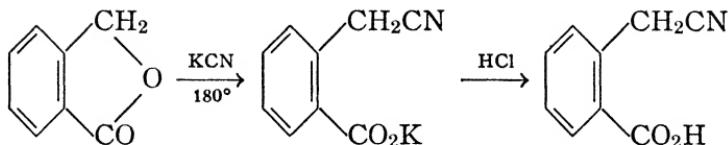
2. Notes.

1. This amount assumes 100 per cent purity. The checkers used 342 g. of 95 per cent sodium hydroxide.
2. This amount assumes 100 per cent purity. The checkers used 288 g. of 92 per cent zinc dust.
3. At the end of this time, the reddish mixture should be free from the odor of nitrobenzene. If it is not, refluxing is continued for two to three hours longer.

3. Methods of Preparation

Azobenzene has been prepared in many different ways. The present method of preparation is a modification of the one used by Alexejew.¹

¹ Alexejew, Z. Chem. 4, 497 (1868).

o*-CARBOXYPHENYLACETONITRILE*(*o*-Toluic Acid, α -cyano-)**

Submitted by CHARLES C. PRICE and RICHARD G. ROGERS.
Checked by W. E. BACHMANN and RICHARD D. MORIN.

1. Procedure

A MIXTURE of 100 g. of phthalide (Note 1) and 100 g. of powdered potassium cyanide is placed in a 2-l. round-bottomed flask fitted with a stirrer and a thermometer. The stirred mixture is heated to 180–190° (internal temperature) for four to five hours in an oil bath (Note 2). One liter of water is added to the cooled mass, and the mixture is stirred until the solid salts are dissolved (Note 3). Any insoluble material which separates is removed by filtration (Note 4). Under a hood, 6 N hydrochloric acid (20–60 cc.) is added to the dark aqueous solution until it becomes turbid (Note 5). The solution is carefully neutralized with sodium bicarbonate (Note 6), a few grams of Norite is added, and the mixture is stirred for several minutes and filtered. The nearly colorless filtrate is acidified with 40–50 cc. of concentrated hydrochloric acid and, after cooling in an ice bath, is filtered with suction. The yield is 80–100 g. (67–83 per cent of the theoretical amount) of white crystals which melt at 113–115° (Note 7).

2. Notes

1. The submitters used phthalide obtained from E. I. du Pont de Nemours and Company, Wilmington, Delaware. The checkers prepared it according to Org. Syn. 16, 71.
2. At the end of the reaction, the mixture should be dark brown and nearly solid. The temperature must not rise above 200°; the checkers kept it at 180°.

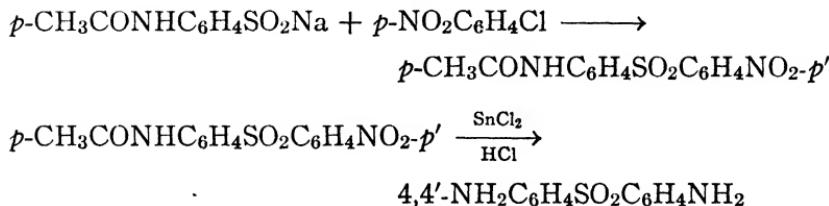
3. About one hour is required to disintegrate the mass.
4. In some cases 5-15 g. of phthalide is recovered at this point.
5. In a few cases, a small amount of crystalline homophthalimide separated from the alkaline solution at this point; m.p. 235°.¹
6. The checkers found it advisable to acidify the solution slightly at this stage in order to precipitate dark impurities.
7. This material is satisfactory for most purposes. It can be purified by recrystallization from benzene or acetic acid, though with considerable loss.

3. Methods of Preparation

This procedure is essentially that of Wislicenus,² which is the only method available.

4,4'-DIAMINODIPHENYLSULFONE

(Aniline, *p,p'*-sulfonylbis-)



Submitted by C. W. FERRY, J. S. BUCK, and R. BALTZLY.
Checked by C. F. H. ALLEN and JAMES VAN ALLAN.

1. Procedure

IN a 1-l. beaker on a steam bath, 155 g. (0.78 mole) of *p*-acetaminobenzenesulfinic acid (Org. Syn. Coll. Vol. 1, 1st Ed. (1932), p. 7; 2nd Ed. (1941), p. 7) is suspended in 310 cc. of water. The

¹ Gabriel, Ber. 19, 1655 (1886).

² Wislicenus, Ann. 233, 102 (1886).

suspension is stirred by hand and warmed gently while it is neutralized by the addition of a solution of 31.5 g. of sodium hydroxide in 125 cc. of water (Note 1). The solution is then transferred to a 2-l. flask and the bulk of the water is removed under the vacuum of a good water pump; 330–350 cc. of water is removed during one and one-half hours. During this time, the solid salt begins to separate. When bumping becomes severe, the flask is cooled by immersion in an ice bath for half an hour, and the salt is filtered with suction. The filtrate is concentrated as before, the product being added to the first crop. The second filtrate, on concentration, yields a less pure salt which may be worked up separately. The yields are 107–124 g. (63–73 per cent of the theoretical amount) of the first crop, 25–34 g. (15–20 per cent) of the second crop, and 12–17 g. (7–10 per cent) of material of inferior grade.

In a 500-cc. three-necked, round-bottomed flask fitted with a reflux condenser, mechanical stirrer, and thermometer are placed 48.5 g. (0.22 mole) of the sodium sulfinate and 60 cc. of a mixture of 75 cc. of ethylene glycol and 120 cc. of carbitol or methyl carbitol. The mixture is stirred and heated in an oil bath until solution is complete, after which 31.5 g. (0.2 mole) of 4-chloronitrobenzene (m.p. 76–78°) is added. The mixture is heated for three and a half hours at 141–143° (thermometer in the mixture), with continued stirring, and then is allowed to cool overnight. After addition of 20 cc. of water, the pasty lumps are broken up, and the solid is filtered with suction and washed with 50–75 cc. of hot water. The solid is then transferred to a 1-l. flask and refluxed with 250 cc. of 95 per cent alcohol for fifteen minutes. After cooling, the *p*-nitro-*p*'-acetylaminodiphenylsulfone is filtered with suction and washed on the funnel, first with 25 cc. of alcohol and then with 25 cc. of ether. After drying in the air, the tan-colored solid weighs 32–33 g. (50–52 per cent of the theoretical amount) and melts at 226–228° (Note 2).

To a solution of 300 g. of stannous chloride dihydrate in 300 cc. of concentrated hydrochloric acid (sp. gr. 1.19) in a 1-l. beaker there is added 96 g. of the sulfone, and the mixture is stirred occasionally. Evolution of heat is sufficiently great so

that, after ten to fifteen minutes, external cooling is necessary to prevent violent boiling with possible loss of material (Note 3). After nearly all the solid has dissolved, the mixture is heated on the steam bath for two hours. The solution is then cooled and added to 1.35 l. of 40 per cent sodium hydroxide solution contained in a 3-l. beaker; it is necessary to stir mechanically and to add about 1.5 kg. of ice during the operation. The final temperature should be about 10°. After standing for a half hour, the crude amine is filtered with suction (Note 4) and washed with water (200–250 cc.) until free from alkali.

The amine is recrystallized by dissolving it in 250 cc. of 95 per cent alcohol, boiling a few minutes with 5 g. of Norite, and filtering. The clear filtrate is either concentrated to a small volume or is diluted by the addition of 200–250 cc. of water (Note 5) and allowed to stand overnight in the icebox. The crystalline amine (m.p. 176°) is then filtered and air-dried. The yield is 55–57 g. (74–77 per cent of the theoretical amount) (Note 6).

2. Notes

1. Frequently the solution develops a blue color. If this persists, a little additional sodium hydroxide solution is required.
2. The yield (per cent) is the same if twice the amounts given are used. It is convenient to combine several runs for the reduction.
3. Sometimes the reduction does not start readily. If this is the case, the beaker may be cautiously heated, but provision for rapid cooling should be made.
4. Filtration is facilitated by use of a Pyrex glass or Vinyon filter fabric; a 30-cm. funnel is advisable.
5. A part of the amine usually crystallizes during the filtration. It is dissolved by warming, after which water is added until the solution is just cloudy.
6. If the melting point is low, a second recrystallization is needed.

3. Methods of Preparation

4,4'-Diaminodiphenylsulfone and/or 4,4'-diacetylaminodiphenylsulfone have been prepared by various procedures, starting with 4,4'-dinitrodiphenylsulfide;¹ or 4,4'-dichlorodiphenylsulfone.^{2, 3} It has also been made from a sulfinic acid and a halonitrobenzene;⁴ from 4-acetylaminobenzenesulfonyl chloride and acetanilide;⁵ from acetanilide and thionyl chloride;⁶ from 4-nitro-4'-aminodiphenylsulfide;⁷ and by acetylation of thioaniline (4,4'-diaminodiphenylsulfide) followed by hydrogen peroxide oxidation.⁸ The 4,4'-diacetylaminodiphenylsulfone obtained by any of these procedures is readily deacetylated.^{7, 8} A method somewhat similar to the one described above has recently been patented.⁹

¹ Fromm and Wittmann, Ber. **41**, 2270 (1908).

² I. G. Farbenind. A-G., Brit. pat. 506,227 [C. A. **33**, 9328 (1939)].

³ I. G. Farbenind. A-G., Fr. pat. 829,926 [C. A. **33**, 1760 (1939)].

⁴ Schering A-G., Brit. pat. 510,127 [C. A. **34**, 4079 (1940)].

⁵ Kereszty and Wolf, Hung. pat. 120,021 [C. A. **33**, 4600 (1939)].

⁶ Sugasawa and Sakurai, J. Pharm. Soc. Japan **60**, 22 (1940) [C. A. **34**, 3704 (1940)].

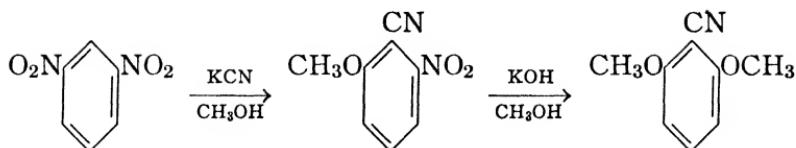
⁷ Raiziss, Clemence, Severac, and Moetsch, J. Am. Chem. Soc. **61**, 2763 (1939).

⁸ Van Arendonk and Kleiderer, J. Am. Chem. Soc. **62**, 3521 (1940).

⁹ Roblyn and Williams, U. S. pat. 2,227,400 [C. A. **35**, 2531 (1941)].

2,6-DIMETHOXYBENZONITRILE

(Benzonitrile, 2,6-dimethoxy-)



Submitted by ALFRED RUSSELL and W. G. TEBBENS.
Checked by R. L. SHRINER and ROBERT S. VORIS.

1. Procedure

(A) *2-Nitro-6-methoxybenzonitrile*.—Five hundred grams (2.97 moles) of technical *m*-dinitrobenzene (m.p. 88–89°) is dissolved in 7.5 l. of absolute methyl alcohol in a 12-l. round-bottomed flask fitted with an efficient mechanical stirrer. The temperature is raised to 40° by means of a water bath and maintained there while a solution of 230 g. of potassium cyanide in 400 cc. of water is added with stirring. The dark purple mixture is stirred for two hours and then is allowed to stand at room temperature for two to three days. The black precipitate is collected with suction on a Büchner funnel, pressed as dry as possible, and then spread out in the air to dry. It weighs about 185–188 g.

The filtrate is diluted with 60 l. of cold water (Note 1) and allowed to stand overnight. The brown sludge is filtered with suction (Note 2) and pressed as dry as possible on the funnel. After drying, it weighs about 164 g. The combined precipitates are refluxed for thirty minutes each with successive 650-, 500-, and 500-cc. portions of chloroform. The chloroform extracts are filtered while hot, and the bright red filtrates are combined and concentrated to a volume of 500 cc. by distillation. One liter of petroleum ether (b.p. 60–90°) is added, whereupon the crude 2-nitro-6-methoxybenzonitrile separates as a red powder. It is removed by filtration and air-dried. It weighs 120–125 g. (22–23 per cent of the theoretical amount) and melts at 148–157° (Note 3). It is used without purification (Note 4).

(B) *2,6-Dimethoxybenzonitrile*.—The crude nitrile is placed in a 3-l. flask and is refluxed for two hours with a solution of 75 g. of potassium hydroxide in 1.9 l. of methyl alcohol. The solution is concentrated by distillation to a volume of 400 cc. and then is poured into 4 l. of cold water. The brownish solid is filtered, washed thoroughly with cold water, and dried. The crude product (85–95 g.) is dissolved in 300 cc. of chloroform and refluxed with 8 g. of Darco for thirty minutes. The hot mixture is filtered, and 500 cc. of hot petroleum ether (b.p. 60–90°) is added to the filtrate. The solution is cooled, and the light-tan-colored needles of 2,6-dimethoxybenzonitrile are removed by filtration. The product weighs 75–86 g. (15–17 per cent of the theoretical amount) and melts at 116–117° (Note 5).

2. Notes

1. The dilution is conveniently carried out by dividing the mixture among seven 3-gal. earthenware crocks.
2. The filtration can be performed by siphoning the mixture from the crocks through an 18.5-cm. Büchner funnel fitted to a 12-l. flask attached to a suction pump.
3. A fourth extraction with 500 cc. of chloroform gives only an additional 4 g. of product.
4. Dioxane is an excellent solvent for cleaning the flasks and crocks used in this first step.
5. This product is pure enough for most purposes. Pure white needles, melting at 117–118°, may be obtained by repeating the crystallization from the chloroform-petroleum ether mixture. The recovery is about 89–90 per cent.

3. Methods of Preparation

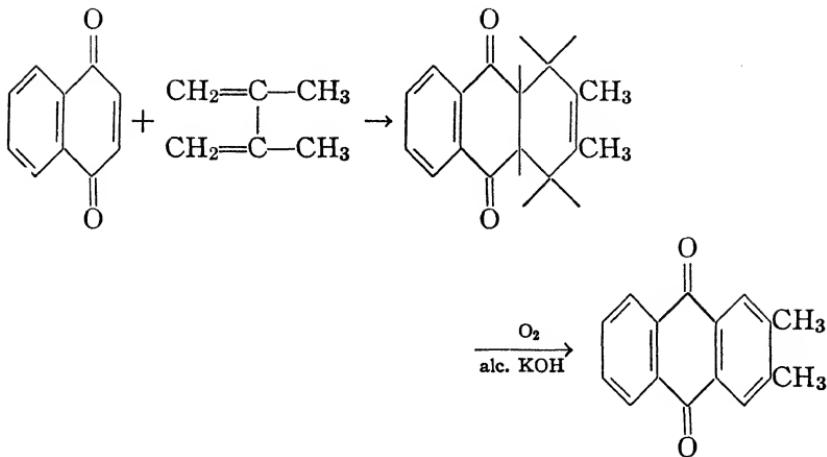
The action of alcoholic potassium cyanide on *m*-dinitrobenzene was first studied by Lobry de Bruyn.¹ The present method is a modification of the procedure described by Mauthner.²

¹ Lobry de Bruyn, Rec. trav. chim. **2**, 205 (1883).

² Mauthner, J. prakt. Chem. (2) **121**, 259 (1929).

2,3-DIMETHYLANTHRAQUINONE

(Anthraquinone, 2,3-dimethyl-)



Submitted by C. F. H. ALLEN and ALAN BELL.

Checked by R. L. SHRINER and JOHN C. ROBINSON, JR.

1. Procedure

A SOLUTION of 80 g. (0.5 mole) of 1,4-naphthoquinone (Org. Syn. Coll. Vol. 1, 1st Ed. (1932), p. 375; 2nd Ed. (1941), p. 383) and 80 g. (1 mole) of 2,3-dimethylbutadiene-1,3 (p. 39) in 300 cc. of alcohol is refluxed for five hours, using a 1-l. round-bottomed flask and an efficient reflux condenser. The solution is cooled and placed in a refrigerator for ten to twelve hours. The crystalline mass is then broken up with a spatula, and the addition product is filtered and washed with 50 cc. of cold alcohol. The product forms white feathery crystals melting at 147–149° (Note 1). The yield is 116 g. (96 per cent of the theoretical amount based on the 1,4-naphthoquinone).

For the dehydrogenation, 40 g. of the addition product is dissolved in 600 cc. of 5 per cent alcoholic potassium hydroxide solution (Note 2) in a 1-l. three-necked flask equipped with a reflux condenser and inlet tube. A current of air is bubbled through

the solution for twenty-four hours; considerable heat is generated, and the initial green color soon changes to yellow. The yellow quinone that has separated is then filtered with suction and is washed, first with 200 cc. of water, then with 100 cc. of alcohol, and finally with 50 cc. of ether. The yield of air-dried product (m.p. 209–210°) is 36.5–37.5 g. (94–96 per cent of the theoretical amount) (Note 3). The over-all yield for both steps is 90 per cent (Note 4).

2. Notes

1. The addition product is usually pure enough for the next step. It may be purified by recrystallization from acetone, ethyl alcohol, or methyl alcohol, and then it melts sharply at 150°. If the crude product is deeply colored, it should be recrystallized, using a decolorizing carbon.
2. This is prepared by dissolving 30 g. of potassium hydroxide in 570 g. of 95 per cent ethyl alcohol.
3. The melting points given in the literature vary from 183°¹ to 208°².
4. Essentially the same percentage yield has been obtained using three times the amounts given.

3. Methods of Preparation

2,3-Dimethylanthraquinone has been obtained by ring closure of the corresponding *o*-benzoylbenzoic acid;^{1, 2, 3} by oxidation of the corresponding anthrone;⁴ from 2-chloro- and 2,3-dichloro-1,4-naphthoquinone and 2,3-dimethylbutadiene-1,3 by the action of sodium hydroxide;⁵ and from 2-methyl-1,4-naphthoquinone and 2,3-dimethylbutadiene-1,3 with subsequent dehydrogenation by sulfur.⁶ The addition product obtained by this procedure, but using a large excess of hydrocarbon, has been described recently.⁷

¹ Elbs and Emich, Ber. **20**, 1361 (1887); J. prakt. Chem. (2) **41**, 6 (1890).

² Heller, Ber. **43**, 2891 (1910).

³ Fairbourne, J. Chem. Soc. **119**, 1573 (1921).

⁴ Limpricht and Martens, Ann. **312**, 103 (1900).

⁵ I. G. Farbenind. A.-G., Ger. pat. 500,160 [Frdl. **17**, 1143 (1932); C. A. **24**, 4790 (1930)].

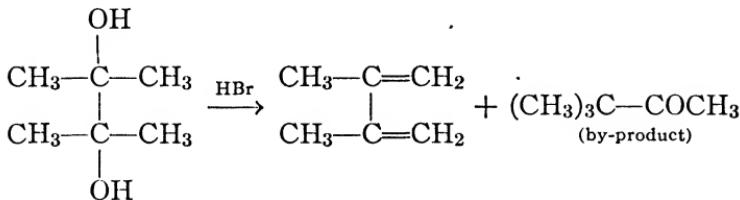
⁶ Fieser and Seligman, J. Am. Chem. Soc. **56**, 2690 (1934).

⁷ Fieser and Webber, J. Am. Chem. Soc. **62**, 1362 (1940).

2,3-DIMETHYLBUTADIENE-1,3

(1,3-Butadiene, 2,3-dimethyl-)

(A) Hydrobromic Acid Method



Submitted by C. F. H. ALLEN and ALAN BELL.

Checked by R. L. SHRINER and JOHN C. ROBINSON, JR.

1. Procedure

IN a 2-l. round-bottomed flask, surmounted by a packed fractionating column (Note 1), is placed a mixture of 354 g. (3 moles) of pinacol (Note 2) and 10 cc. of commercial 48 per cent hydrobromic acid. A few boiling chips are added, and the flask is then heated slowly with a colorless flame about 3 in. high (Note 3). The distillate is collected until the thermometer reads 95°; this requires about two hours when the rate of distillation is approximately twenty to thirty drops per minute. The upper, non-aqueous layer is washed twice with 100-cc. portions of water, 0.5 g. of hydroquinone is added, and the liquid is dried overnight with 15 g. of anhydrous calcium chloride. It is then fractionated as below, using the same column but a 1-l. flask (Note 4).

YIELD			
FRACTION	B.P.	Grams	Per Cent
2,3-Dimethylbutadiene	69-70.5°	135-147	55-60
Intermediate	70.5-105°	10-15	
Pinacolone	105-106°	66-75	22-25
Residue		7-8	

2. Notes

1. The column described in Org. Syn. 20, 96 (Note 1), filled with glass helices, and wrapped with asbestos paper, is satisfactory. Carborundum may also be used as the filling, but a longer

time is required for the distillation. Cold water is circulated through the cold finger.

2. The pinacol used was the commercially available material, or that obtained by dehydration of pinacol hydrate. This dehydration may be accomplished by adding 2 l. of benzene to 1 kg. of pinacol hydrate (Org. Syn. Coll. Vol. 1, 1st Ed. (1932), p. 448; 2nd Ed. (1941), p. 459), and distilling the water-benzene mixture. The lower layer is separated, and the upper benzene layer is returned to the distilling flask. This is repeated until the benzene distillate is clear. The anhydrous pinacol is then distilled, and the fraction boiling from 168° to 173° is collected. Depending upon the quality of the material used, 1 kg. of pinacol hydrate yields about 500 g. of anhydrous pinacol.

3. If too large a flame is used the column floods.

4. 2,3-Dimethylbutadiene can be kept, without appreciable change, for a limited time in a refrigerator. If it is not to be used reasonably soon, it is advisable to add a little hydroquinone as an inhibitor.

(B) Aluminum Oxide Method

Submitted by L. W. NEWTON and E. R. COBURN.

Checked by NATHAN L. DRAKE and RICHARD TOLLEFSON.

1. Procedure

A CLAISEN FLASK, provided with the usual capillary inlet for air, is connected to a Pyrex tube (Note 1) which is drawn out at one end and packed with 8-mesh alumina (Note 2). The tube is inserted in an electric furnace (Note 3) capable of maintaining a temperature of 420–470°; the temperature is measured by a thermometer placed alongside the tube in the furnace. The drawn-out end of the tube is connected by a rubber stopper to an efficient Pyrex coil-condenser, which is in turn connected by a rubber stopper to the first of two receivers, arranged in series and connected by a short length of rubber tubing. Each receiver consists of a 500-cc. filter flask, which carries an inlet tube (Note 4) extending somewhat more than halfway to the bottom of the flask. The first receiver is immersed in an ice-salt mixture

(Note 5); the second is immersed in a Dry Ice-methanol mixture contained in a Dewar flask. The exit tube of the second receiver is connected to a manometer (Note 6) and to a water pump.

Pinacol (Note 7) or pinacolone is placed in the Claisen flask and is distilled, under the vacuum of a water pump, through the Pyrex tube, which is maintained at a temperature of 420-470°. About 100 g. of pinacol is distilled in fifteen minutes, and then the apparatus is swept out by maintaining the reduced pressure for fifteen minutes longer. The water and resinous material collected in the ice-cooled receiver are discarded (Note 8). The second receiver is removed from the cooling bath, and the product is allowed to melt. Two layers are formed; these are allowed to separate, and then the receiver is replaced in the cooling bath until the lower water layer is frozen. The crude dimethylbutadiene is then decanted. The yellow product is dried over anhydrous calcium sulfate and is fractionated (Note 9) through a Widmer or other column; the portion boiling at 67-70° is collected. The yield from 100 g. of pinacol is 55-60 g. (79-86 per cent of the theoretical amount) (Note 10). The diene is best stored over a small amount of hydroquinone in a refrigerator.

2. Notes

1. The Pyrex tube should have a diameter of 3 cm. and a length of 70 cm.
2. The grade of alumina is important. With an ordinary grade of desiccator alumina, the checkers were unable to obtain the yields stated. The alumina employed successfully was Alorco activated alumina, from the Aluminum Ore Company, East St. Louis, Illinois. The catalyst darkens in use, but it can be kept in a clean and active condition by the following treatment: after each run, or at least after two or three runs, the tube is heated to 420-470°, and a slow stream of air is drawn through it until the alumina is white (two to five hours).

3. A very convenient furnace can be constructed by wrapping a 3-ft. length of 1½-in. iron pipe with asbestos paper and winding a suitable heating element over this paper (about 47.5 ft. of No. 18 B. & S. gauge Nichrome wire). The whole is enclosed in a

length of steam-pipe insulation. The temperature is controlled by a properly chosen Variac (variable transformer).

4. The inlet tube should have a diameter of 10 mm.
5. This receiver serves to collect most of the water and polymer formed.
6. Another receiver, consisting of a 3 by 30 cm. side-arm test tube, may be used. It is immersed in a Dewar flask and cooled with Dry Ice-methanol. Only a small amount of material is collected in this receiver.

7. Anhydrous pinacol can be prepared from pinacol hydrate (Org. Syn. Coll. Vol. 1, 1st Ed. (1932), p. 448; 2nd Ed. (1941), p. 459) by distillation. The material which boils at 172–178° is collected, and the distillate should be refractionated. It is more convenient, however, to prepare anhydrous pinacol from the hydrate by the method described in Note 2 under part A (p. 40). Pinacol hydrate may be used as starting material; the yield will be slightly less than that obtained when the anhydrous material is used.

8. The contents of this receiver should be examined carefully for the presence of 2,3-dimethylbutadiene; the checkers usually found appreciable amounts present.

9. If the dehydration has been inefficient, some pinacolone (b.p. 107°) may be present in this product. The pinacolone may be distilled over the alumina again.

10. According to the submitters, the yield from 100 g. of pinacolone is 57–63 g. (70–77 per cent of the theoretical amount.)

3. Methods of Preparation

The most convenient method for preparation of 2,3-dimethylbutadiene involves the dehydration of pinacol. Many catalysts have been used, among them hydrobromic,¹ hydriodic,¹ and sulfuric acids;^{2, 3, 4} sulfonic acids of the benzene⁵ and naphtha-

¹ Kyriakides, J. Am. Chem. Soc. **36**, 985 (1914).

² Bayer and Company, Ger. pat. 253,081 [Frdl. **10**, 1006 (1910–1912)].

³ Couturier, Ann. chim. (6) **26**, 485 (1892).

⁴ Kondakow, J. prakt. Chem. (2) **62**, 172 (1900).

⁵ Ostromisslenski, J. Russ. Phys. Chem. Soc. **47**, 1973 (1915) [C. A. **10**, 1341 (1916)].

lene^{6, 7, 8} series; acid potassium sulfate;⁹ alum;¹⁰ aniline hydrobromide;¹ iodine;¹¹ hot copper at 450–480°;¹ and alumina at 400°.^{12, 13, 14} The diene has also been obtained by distillation of the product from the reaction between methylmagnesium iodide and ethyl α -methacrylate;¹⁵ by treatment of tetramethylethylene dichloride with alcoholic potash;⁴ from pinacol hydrochloride and sodium carbonate;¹⁶ by the action of sodium or pyridine on α, α, β -trimethyl- $\beta\gamma$ -dibromobutyric acid;¹⁷ by passing 1,2,4-trimethyl-4-isopropenylcyclohexene over hot copper;¹⁸ and by dehydration of dimethylisopropenylcarbinol with hydrochloric¹⁹ or sulfuric acid.¹⁷

⁶ Bayer and Company, Ger. pat. 249,030 [Frdl. **10**, 1004 (1910–1912); C. A. **6**, 3200 (1912)].

⁷ Bayer and Company, Ger. pat. 253,082 [Frdl. **10**, 1005 (1910–1912); C. A. **7**, 1109 (1913)].

⁸ Ruzicka and Schinz, Helv. Chim. Acta **23**, 963 (1940).

⁹ Bayer and Company, Ger. pat. 246,660 [Frdl. **10**, 1003 (1910–1912); C. A. **7**, 908 (1913)].

¹⁰ Bayer and Company, Ger. pat. 250,086 [Frdl. **10**, 1005 (1910–1912); C. A. **6**, 3200 (1912)].

¹¹ Hibbert, J. Am. Chem. Soc. **37**, 1754 (1915).

¹² Badische Anilin- u. Soda-Fabrik, Ger. pat. 235,311 [Frdl. **10**, 1003 (1910–1912); C. A. **5**, 3175 (1911)].

¹³ Badische Anilin- u. Soda-Fabrik, Ger. pat. 256,717 [Frdl. **11**, 796 (1912–1914); C. A. **7**, 2488 (1913)].

¹⁴ Fieser and Martin, J. Am. Chem. Soc. **59**, 1019 (1937); Fieser and Seligman, ibid. **56**, 2694 (1934); Fieser, Experiments in Organic Chem., 2nd Ed., p. 383, D. C. Heath and Co., New York, 1941.

¹⁵ Blaise and Courtot, Compt. rend. **140**, 371 (1905).

¹⁶ Harries, Ann. **383**, 182 (1911).

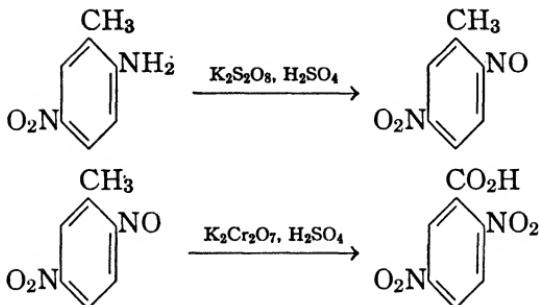
¹⁷ Courtot, Bull. soc. chim. (3) **35**, 972 (1906).

¹⁸ Ostromisslenski, J. Russ. Phys. Chem. Soc. **47**, 1949 (1915) [Chem. Zentr. **1916**, I, 1133; C. A. **10**, 1340 (1916)].

¹⁹ Marinca, J. Russ. Phys. Chem. Soc. **21**, 435 (1889) [Chem. Zentr. **1890**, I, 520].

2,5-DINITROBENZOIC ACID

(Benzoic Acid, 2,5-dinitro-)



Submitted by WILSON D. LANGLEY.

Checked by W. E. BACHMANN and D. W. HOLMES.

1. Procedure

(A) *2-Nitroso-5-nitrotoluene*.—In a 5-l. round-bottomed flask fitted with a mechanical stirrer is placed 50 g. (0.33 mole) of pulverized 5-nitro-2-aminotoluene (Note 1). To this is added an ice-cold solution of 200 cc. of concentrated sulfuric acid in 50 cc. of water. While the suspension is stirred at room temperature, a solution of Caro's acid is prepared, as follows: to 175 cc. of ice-cold sulfuric acid (sp. gr. 1.84) in a 2-l. beaker is added 300 g. (1.11 moles) of pulverized potassium persulfate. The mixture is thoroughly stirred with a glass rod, and to it is added 900 g. of crushed ice and 300 cc. of water.

The well-stirred solution of Caro's acid is poured into the suspension of nitroaminotoluene. The mixture is stirred and warmed, but as soon as the temperature reaches 40°, heating is discontinued. After the solution has been stirred for two hours longer, an additional 100 g. (0.37 mole) of powdered potassium persulfate is added in one portion. The heat of reaction is sufficient to maintain the temperature at 40°. Stirring is continued for two hours more, and the suspension is then diluted with water to 4 l. The solid is filtered with suction (Note 2) and washed with 400 cc.

of water. The wet material is transferred to a 5-l. round-bottomed flask, about 700 cc. of water is added, and the mixture is steam-distilled. The 2-nitroso-5-nitrotoluene is filtered from the distillate (Note 3). The total yield of air-dried product is 30-39 g. (55-71 per cent of the theoretical amount) (Note 4).

(B) *2,5-Dinitrobenzoic Acid*.—A suspension of 20 g. (0.12 mole) of the air-dried 2-nitroso-5-nitrotoluene in 100 cc. of water is prepared in a 500-cc. Erlenmeyer flask, and to it is added 50 g. (0.17 mole) of powdered potassium dichromate (Note 5). The flask is placed in an ice-salt bath, and the mixture is stirred vigorously by means of an efficient stirrer. When the temperature has dropped to 5°, 175 cc. of concentrated sulfuric acid is added in a thin stream (Note 6), while the temperature is not allowed to exceed 35°. After all the sulfuric acid has been added the mixture is stirred and heated to 50°. The source of heat is removed, and the temperature is maintained between 50° and 55° by cooling in an ice bath as the exothermic reaction takes place (Note 7). After twenty minutes the temperature is raised to 65°±3°, and held there for one hour longer.

The solution is cooled to 20°, and 250 g. of ice is added. The mixture is stirred for a few minutes, then is filtered with suction (hardened filter paper), and the solid is washed with 35 cc. of ice-water. The solid is suspended in 25 cc. of water in a 600-cc. beaker and is slowly dissolved by gradual addition of 55-65 cc. of a 10 per cent solution of sodium carbonate. The solution is filtered (Note 8), and the filtrate is made strongly acidic to Congo red by addition of 1:1 hydrochloric acid. The mixture is chilled in ice for an hour and is then filtered. The product is washed with 12 cc. of ice-water and air-dried. The acid melts at 174-176° and weighs 14-17 g. (55-66 per cent of the theoretical amount). The acid may be recrystallized by dissolving 10 g. of it in 250 cc. of boiling 5 per cent hydrochloric acid (Note 9). The solution, when chilled in ice, deposits 9.4 g. of 2,5-dinitrobenzoic acid as nearly colorless crystals which melt at 177-178° (Note 10).

2. Notes

1. Eastman Kodak Company's Practical grade was used.
2. The filtrates, on standing overnight, deposit 5-5.6 g. of crude 2-nitroso-5-nitrotoluene, which is not included in the weights recorded. It may be added to the product obtained by steam distillation.
3. The submitters reported that successive 2.5-l. portions of distillate were filtered, and the following weights of product were obtained: 14.5, 10.7, 9.0, and 2 g., or 36.2 g. in 10 l. From one run the checkers obtained 19, 12, 6, and 2 g., or 39 g. In some runs it was necessary to collect 15-30 l. of distillate in order to obtain a 30-g. yield. The submitters report that unchanged amine, if present during the steam distillation, condenses with the nitroso compound, giving tarry products, and the yield of nitroso compound is reduced.
4. In favorable cases, the product is white and melts at 135-136°.
5. The procedures given in Org. Syn. Coll. Vol. 1, 1st Ed. (1932), pp. 385, 528; 2nd Ed. (1941), pp. 392, 543, are not suitable for the oxidation of nitrosonitrotoluenes. Using the procedure given on p. 385 of the 1st Ed. (2nd Ed., p. 392) the yield of dinitro acid is low, and using the procedure given on p. 528 of the 1st Ed. (2nd Ed., p. 543) the dinitro acid is deeply colored.
6. This requires twenty to twenty-five minutes.
7. In a run twice this size the checkers observed that at this stage some of the semi-solid material on the top of the stirred solution burned. The burning ceased after a few minutes. The yield of final product was slightly lower. It must be emphasized that careful control of the temperature is necessary during the oxidation with dichromate in order to prevent the reaction from becoming too vigorous.
8. The undissolved residue is largely 2,5-dinitrotoluene, which may be used in subsequent oxidations. Larger yields of this compound may be obtained by shortening the time of stirring during the oxidation process.

9. Additional data on the recrystallization of 2,5-dinitrobenzoic acid are: a solution of 6.83 g. in 200 cc. of boiling toluene, when filtered and chilled, furnished 5.9 g.; a solution of 10 g. in 110 cc. of boiling water, when filtered and chilled, furnished 9.18 g.

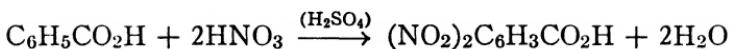
10. When 3-nitro-4-aminotoluene was used, 3,4-dinitrobenzoic acid was obtained in approximately the same yields as those recorded for 2,5-dinitrobenzoic acid. The submitter reports: "3-nitro-4-aminotoluene dissolves readily in the sulfuric acid when the Caro's acid is added, and the 3-nitro-4-nitrosotoluene which separates is practically free of the amine. Therefore, the steam distillation may be omitted and the nitroso compound may be oxidized directly to the dinitro acid, which is obtained as a light-colored product. From 100 g. of 3-nitro-4-aminotoluene there was obtained 102 g. of yellow nitrosonitrotoluene which, when oxidized, gave 85 g. of 3,4-dinitrobenzoic acid melting at 158-162°. One crystallization gave the pure acid. A solution of 10 g. of the acid in 210 cc. of boiling water gave, after cooling, 9.1 g. of the acid. Similarly, a solution of 10 g. of the acid in 280 cc. of hot 5 per cent hydrochloric acid was filtered quickly and then cooled. The filtrate deposited 9.4 g. of the acid."

3. Methods of Preparation

2,5-Dinitrobenzoic acid has been prepared by nitration of *o*-nitrobenzoic acid and fractional crystallization of the acids as the barium salts;¹ and by oxidation of 2,5-dinitrotoluene.²

¹ Griess, Ber. 7, 1223 (1874).

² Grell, Ber. 28, 2564 (1895).

3,5-DINITROBENZOIC ACID**(Benzoic Acid, 3,5-dinitro-)**

Submitted by (A) R. Q. BREWSTER and BILL WILLIAMS.
 (B) ROSS PHILLIPS.

Checked by HOMER ADKINS and JAMES RUHOFF.

1. Procedure

(A) In a 2-l. round-bottomed flask are placed 61 g. (0.5 mole) of benzoic acid and 300 cc. of concentrated sulfuric acid (sp. gr. 1.84). To this mixture is added 100 cc. of fuming nitric acid (sp. gr. 1.54) in portions of 2 or 3 cc. The temperature during the addition of the acid is kept between 70° and 90° by means of external cooling with cold water (Note 1), and the addition should be carried out in a good hood. The flask is covered with a watch glass and allowed to stand for an hour, or overnight, in the hood. The flask is then heated on a steam bath in the hood for four hours, during which time considerable amounts of brown fumes are evolved. The reaction mixture is then allowed to cool to room temperature (Note 2), whereupon yellow crystals separate from the solution. An additional 75 cc. of fuming nitric acid is added, and the mixture is heated on the steam bath for three hours and then in an oil bath at 135–145° for three hours (hood). Brown fumes are evolved continuously, especially during the heating in the oil bath. The color of the reaction mixture is light to reddish yellow.

The mixture is allowed to cool and is poured into 800 g. of ice and 800 cc. of water. After standing for thirty minutes the 3,5-dinitrobenzoic acid is filtered with suction and washed with water until free of sulfates. The crude product weighs 62–65 g. and melts at 200–202°. This product is recrystallized from 275 cc. of hot 50 per cent ethyl alcohol. The purified 3,5-dinitrobenzoic acid weighs 57–61 g. (54–58 per cent of the theoretical amount) and melts at 205–207° (Note 3).

(B) TWO HUNDRED GRAMS of benzoic acid (1.6 moles) is stirred into a liter of concentrated sulfuric acid contained in a 3-l. round-bottomed flask. The flask is surrounded by cold water, and the temperature is maintained below 45° while 80 cc. of fuming nitric acid is added. When the temperature of the reaction mixture has fallen to 30°, 240 cc. of fuming nitric acid is added, a beaker is inverted over the neck of the flask, and the mixture is allowed to stand for six weeks.

The flask is heated on a steam bath for four hours and then in an oil bath at 145° until all the crystals are dissolved. A mush of crystals separates when the mixture is cooled to room temperature. These are filtered on a Büchner funnel without any filtering medium. After the crystals are pressed dry, they are placed in 1.5 l. of cold water, washed thoroughly, filtered through paper, and dried in the air. The yield is 200–213 g. (60 per cent of the theoretical amount), and the product melts at 205–207° (corr.) (Note 4).

2. Notes

1. The temperature is so controlled that evolution of brown fumes, in other than small quantities, is avoided.
2. Mechanical stirring is advantageous but not necessary.
3. The melting points were taken with a short-stem total-immersion thermometer.
4. Procedure B has been carried out on ten times the scale specified, with yields a few per cent higher than those given above.

3. Methods of Preparation

3,5-Dinitrobenzoic acid has been prepared by nitration of benzoic acid with sulfuric acid and fuming nitric acid;¹ by nitration of 3-nitrobenzoic acid;² and by oxidation of 3,5-dinitrotoluene.^{1, 3} It has been obtained along with other products by the action of nitric acid upon 1,5-dinitronaphthalene.⁴

¹ Cahours, *Jahresber. Fortsch. Chem.* 1847–1848, 533; Voit, *Ann.* **99**, 104 (1856); Michler, *Ann.* **175**, 152 (1875); Hübner, *Ann.* **222**, 72 (1884).

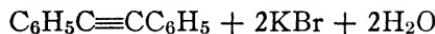
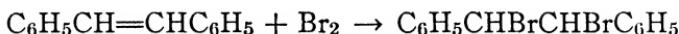
² Tiemann and Judson, *Ber.* **3**, 224 (1870).

³ Staedel, *Ann.* **217**, 194 (1883).

⁴ Beilstein and Kuhlberg, *Ann.* **202**, 220 (1880).

DIPHENYLACETYLENE

(Tolan)



Submitted by LEE IRVIN SMITH and M. M. FALKOF.

Checked by W. E. BACHMANN and CHARLES E. MAXWELL.

1. Procedure

A SOLUTION of 45 g. (0.25 mole) of *trans*-stilbene in 750 cc. of ether is prepared in a 1-l. three-necked, round-bottomed flask fitted with a reflux condenser, an efficient mechanical stirrer, and a dropping funnel. To the well-stirred solution there is added 13.8 cc. (43 g.; 0.27 mole) of bromine, during the course of ten minutes. A solid begins to separate in five minutes, but stirring is continued for one hour. The product is collected on a Büchner funnel and washed with ether until it is white. The yield of stilbene dibromide, melting at 235–237°, is 65.8–69.1 g. (77–81 per cent of the theoretical amount).

A solution of 90 g. of potassium hydroxide in 150 cc. of absolute ethanol is prepared in a 500-cc. round-bottomed flask fitted with a reflux condenser (Note 1). The solution is cooled somewhat, and the stilbene dibromide is added in several portions (Note 2). The mixture is then refluxed for twenty-four hours in an oil bath (Note 3). The hot mixture is poured into 750 cc. of cold water, and the product is removed by filtration and washed with 50 cc. of water. The crude diphenylacetylene is dried over calcium chloride in a vacuum desiccator for eighteen hours at room temperature. The chunky, pale yellow crystals melt at 58–60° and weigh 33.7–37.8 g. By recrystallization of this product from 50 cc. of 95 per cent ethanol there is obtained 29.2–30.5 g. (66–69 per cent of the theoretical amount based on the stilbene)

of pure diphenylacetylene, which forms white needles melting at 60–61° (Note 4).

2. Notes

1. Complete solution of the alkali in the alcohol is effected by placing the flask in an oil bath at 130–140°.
2. The addition of the stilbene dibromide causes an immediate, vigorous reaction, with the evolution of heat. It is necessary to replace the reflux condenser after each addition, until boiling has ceased.
3. An electrically heated oil bath is used to maintain a constant bath temperature of 130–140°.
4. The submitters obtained the same percentage yield on runs four times this size; the time employed was the same as that described here, except for the addition of bromine, which required thirty minutes.

3. Methods of Preparation.

Diphenylacetylene has been prepared by the present method;¹ by the action of sodium amide on monochlorostilbene;² by the action of potassium amide on stilbene dichloride;³ by heating 1,1-diphenyl-2-chloroethane with sodium ethoxide in a sealed tube;⁴ and from benzil via the hydrazone.⁵

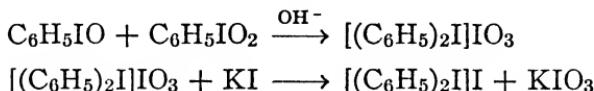
¹ Smith and Hoehn, *J. Am. Chem. Soc.* **63**, 1180 (1941); Söderbäck, *Ann.* **443**, 161 (1925).

² Paillard and Wieland, *Helv. Chim. Acta* **21**, 1363 (1938).

³ Coleman and Maxwell, *J. Am. Chem. Soc.* **56**, 133 (1934).

⁴ Buttenberg, *Ann.* **279**, 327 (1894).

⁵ Schlenk and Bergmann, *Ann.* **463**, 76 (1928).

DIPHENYLIODONIUM IODIDE**(Iodonium Compounds, diphenyl—iodide)**

Submitted by H. J. LUCAS and E. R. KENNEDY.
 Checked by JOHN R. JOHNSON and M. W. FORMO.

1. Procedure

A MIXTURE of 22 g. (0.1 mole) of iodosobenzene (p. 70), 24 g. (0.1 mole) of iodoxybenzene (p. 72), and 200 cc. of 1 *N* sodium hydroxide (Note 1) is gently stirred for twenty-four hours. The resulting brown slurry is thoroughly stirred with 1 l. of cold water, and, after the mixture settles, the supernatant solution of diphenyliodonium iodate is decanted through a filter. The solid residue is extracted twice with 500-cc. portions of water, and the extracts are separated, by decantation through a filter, from the small amount of tarry residue. An aqueous solution of 20 g. (0.12 mole) of potassium iodide is added to the combined filtrates. After the bulky white precipitate of diphenyliodonium iodide has stood for an hour or two, with occasional shaking, it is filtered with suction, washed with water, and dried on porous tile at room temperature. The product weighs 29–30 g. (70–72 per cent of the theoretical amount) and melts at 172–175° with vigorous decomposition.

2. Note.

1. Since the reaction is catalyzed by hydroxide ions, the amount of base may be varied within wide limits. It is advantageous to grind the solid reactants with 50 cc. of water before the alkali is added.

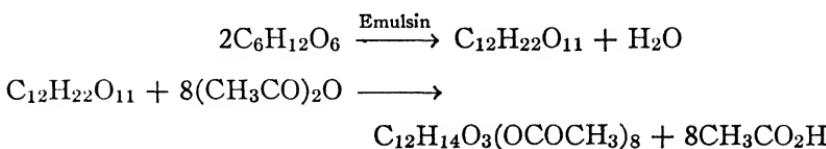
3. Methods of Preparation

Diphenyliodonium iodide is obtained when sulfur dioxide or aqueous potassium iodide is added to a solution containing di-

phenyliodonium iodate.^{1, 2} Such solutions have been prepared by the action of moist silver oxide, or of aqueous sodium or potassium hydroxide, on an equimolar mixture of iodosobenzene and iodoxybenzene;^{1, 2} by shaking iodosobenzene with moist silver oxide;³ by shaking iodoxybenzene with sodium hydroxide;² and by steam distillation of a mixture of iodosobenzene and iodoxybenzene.² Diphenyliodonium iodide has been prepared by heating iodoxybenzene with aqueous potassium iodide and barium hydroxide.⁴

β -GENTIOBIOSE OCTAACETATE

(Gentiobiose, β -octaacetyl-)



Submitted by B. HELFERICH and J. F. LEETE.
Checked by HOMER ADKINS and E. E. BOWDEN.

1. Procedure

A SOLUTION of 1.65 kg. of crystallized glucose or 1.5 kg. of anhydrous glucose (8.3 moles) is prepared by heating the solid on a steam bath with 1.35 l. of distilled water. The solution is cooled and placed in a 2.5-l. glass-stoppered bottle. Fifteen grams of emulsin (Note 1) is added, then 20 cc. of toluene, and the flask is closed and allowed to stand at room temperature, with occasional shaking, for five weeks. The solution is then boiled, diluted with 8.5 l. of water, and filtered. To the filtrate is added 56 g. of baker's yeast in 650 cc. of water, and the temperature of the mixture is maintained at 28–32° for twelve to fourteen days.

¹ Hartmann and Meyer, Ber. 27, 504, 506 (1894).

² Hartmann and Meyer, Ber. 27, 1598 (1894).

³ Hartmann and Meyer, Ber. 27, 503 (1894).

⁴ Willgerodt, Ber. 29, 2009 (1896).

(Note 2). The mixture is then boiled for thirty minutes with an excess of powdered calcium carbonate and filtered.

The filtrate is evaporated under a pressure of 20-30 mm. to as thick a syrup as possible. For this operation the solution is placed in a 12-l. flask set in a steam bath and connected by a goose-neck to a condenser, which in turn is connected to a suction or distilling flask. A very fine capillary inlet tube into the 12-l. flask prevents any violent ebullition (Notes 3 and 4).

To the thick syrup (170-185 g.) are added 100 g. of anhydrous sodium acetate and 1.125 l. of acetic anhydride. The mixture is carefully heated to the boiling point with provision for cooling the flask with wet cloths should the acetylation become too violent. When the reaction is complete (about twenty minutes is required) the solution is poured into 10 l. of ice water. The water is decanted and renewed twice at 24-hour intervals in order to render the acetylated sugar filterable.

The dark brown product is filtered and, after drying in the air, is extracted with ether in a Soxhlet apparatus. The ether is removed by evaporation, and the light-colored residue (170 g.) is recrystallized from 1.65 l. of hot methanol. The crystals are washed on a Büchner funnel with methanol until free from colored impurities. The yield is 77-87 g. of material which melts at 187-190°. A second recrystallization from methanol (1.25 cc. per g. of product) gives pure β -octaacetylgentiobiose, with about 10 per cent loss. The pure substance melts at 196° (corr.).

2. Notes

1. A commercial sample of emulsin was purchased from Merck and Company, Inc. If freshly prepared emulsin of good quality is available, the quantity may be reduced to one-tenth or less of the specified amount.

2. The yeast, by fermentation, removes the glucose which has not been transformed into gentiobiose. Fleischmann's and "Red Star" yeast have been used. The flask should be stoppered and protected with the conventional trap for the escape of carbon dioxide.

3. The submitters suggest a more complicated apparatus (Note 4) for this operation. However, the checkers have had no trouble with foaming or bumping when using the simple apparatus described above. Very little water condenses in the receiver, which serves as a safety trap in case foaming or bumping should occur.

4. The submitters used quantities four times as large as those stated above. They give the following directions for the distillation:

"The solution is drawn slowly through a glass tube provided with a stopcock into a 3-l. distillation flask standing in a bath of rapidly boiling water. The small portion which foams over is collected and evaporated in a second 3-l. distillation flask, likewise standing in rapidly boiling water. The distillate is passed through an efficient condenser and is collected in a thick-walled bottle or flask to which the vacuum pump or water pump is connected. A high vacuum is essential. The tube connecting the condenser and the receiver is provided with a stopcock so that the distillate may be poured out without interrupting the vacuum to any extent."

3. Methods of Preparation

The chief methods for the preparation of gentiobiose and its octaacetate are discussed in a recent paper by Reynolds and Evans.^{1, 2} These methods involve isolation of the substance from gentian root;^{3, 4} the action of emulsin on glucose;^{5, 6} the catalytic hydrogenolysis of amygdalin;⁷ separation from the mother liquors ("Hydrol") obtained in the manufacture of glucose;⁸ and the condensation of acetobromoglucose with β -d-glucose-

¹ Reynolds and Evans, J. Am. Chem. Soc. **60**, 2559 (1938).

² Haworth and Wylam, J. Chem. Soc. **1923**, 123.

³ Bourquelot and Hérissey, Compt. rend. **132**, 571 (1901).

⁴ Bourquelot and Hérissey, Bull. soc. chim. (3) **29**, 363 (1903).

⁵ Bourquelot and Hérissey, Compt. rend. **157**, 732 (1913).

⁶ J. F. Leete, Ph.D. dissertation, Univ. of Greifswald, 1929.

⁷ Bergmann and Freudenberg, Ber. **62**, 2783 (1929).

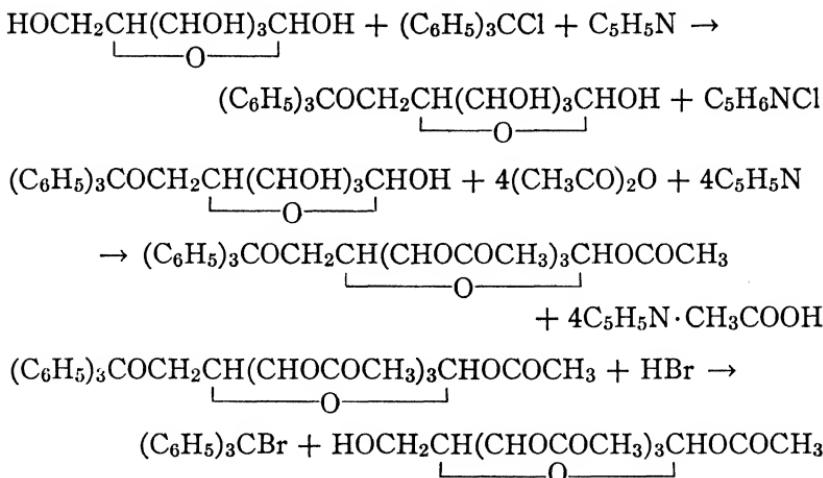
⁸ Berlin, J. Am. Chem. Soc. **48**, 2627 (1926).

1,2,3,4-tetraacetate.^{1, 9} Reynolds and Evans recommend the last-mentioned method.

The method given above is a modification of those originally described by Bourquelot³ and Zemplén.¹⁰

β -d-GLUCOSE-1,2,3,4-TETRAACETATE

(d-Glucose, β -tetraacetyl-)



SUBMITTED by DELBERT D. REYNOLDS and WILLIAM LLOYD EVANS.

Checked by LEE IRVIN SMITH, R. T. ARNOLD, NEWMAN BORTNICK, AARON LERNER, and EVERETT SCHULTZ.

1. Procedure

(A) *6-Trityl- β -d-glucose-1,2,3,4-Tetraacetate*.—A mixture containing 120 g. (0.67 mole) of anhydrous glucose, 193.2 g. (0.7 mole) of trityl chloride, and 500 cc. of anhydrous pyridine (Org. Syn. **21**, 90; Coll. Vol. 1, 1st Ed. (1932), p. 94; 2nd Ed. (1941), p. 100) is heated on the steam cone until solution is complete (Note 1). Without cooling, 360 cc. of acetic anhydride is added

⁹ Helferich and Klein, Ann. **450**, 219 (1926).

¹⁰ Zemplén, Ber. **48**, 232 (1915).

in one portion (Note 2). After standing for twelve hours, the reaction mixture is poured slowly into 10 l. of ice water, to which 500 cc. of acetic acid has been added, and the resulting mixture is vigorously stirred mechanically for two hours (Note 3). The precipitate is filtered and is immediately stirred for a short time with 10 l. of ice water. The white, granular precipitate is filtered, washed well with cold water, and then air-dried (Note 4). The dried solid is digested with 500 cc. of ether (Note 5). The insoluble portion is dissolved in hot 95 per cent ethyl alcohol (approximately 3 l.), and the solution is decolorized and filtered while hot. The filtrate, upon cooling, deposits fine needles of 6-trityl- β -d-glucose-1,2,3,4-tetraacetate of sufficient purity for further use. The yield at this point is about 169 g. (43 per cent of the theoretical amount). Recrystallization from 95 per cent ethyl alcohol gives the pure compound which melts at 166–166.5°. In pyridine, $[\alpha]_D^{19}$ is +44.8°; $[\alpha]_D^{28}$, +45.3°. The yield of purified material is 137 g. (35 per cent of the theoretical amount (Note 6).

(B) β -d-Glucose-1,2,3,4-Tetraacetate.—A solution of 46 g. (0.078 mole) of 6-trityl- β -d-glucose-1,2,3,4-tetraacetate in 200 cc. of acetic acid is prepared by warming on the steam bath. The solution is then cooled to approximately 10°, 18 cc. of a saturated solution of dry hydrogen bromide in acetic acid is added, and the reaction mixture is shaken for about forty-five seconds. The trityl bromide formed during the reaction is removed *at once* by filtration, and the filtrate is poured *immediately* into 1 l. of cold water. The tetraacetate is extracted with 250 cc. of chloroform; the chloroform extract is washed four times with ice water and dried over anhydrous sodium sulfate. The drying agent is removed, and the chloroform is evaporated, under reduced pressure at room temperature. The remaining syrup is covered with 100 cc. of anhydrous ether and is rubbed with a glass rod. Crystallization takes place immediately. The product is removed and is purified by dissolving it in the minimum amount of chloroform and adding anhydrous ether until crystallization begins. The purified product melts at 128–129°. In chloroform, $[\alpha]_D^{20}$ is +12.1°. The yield is 15 g. (55 per cent of the theoretical amount).

2. Notes

1. The materials and apparatus used for this reaction must be strictly anhydrous in order to prevent hydrolysis of the trityl chloride.
2. Higher temperatures favor formation of the β -isomer.
3. The stirring must be unusually rapid, and the solution must be added to the water slowly and in a fine stream. If this is not done, the precipitate will not be granular and will be extremely difficult to filter.
4. If the material warms up to room temperature during the time required for drying, it becomes exceedingly sticky, and mechanical difficulties in manipulation result. This behavior appears to be due to the presence of traces of pyridine. The checkers found that the pure product, m.p., 166–166.5°, when recrystallized from pyridine, gave a sticky material.
5. The α -isomer is soluble in ether, whereas the β -isomer is insoluble. In some cases the entire product dissolves, but the β -isomer separates when the solution is allowed to stand.
6. The submitters state that the yield of purified product varies from 148 to 180 g.

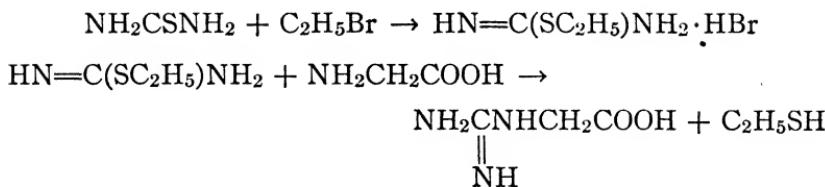
3. Methods of Preparation

These directions are modifications of the methods used by Helferich and Klein for the original preparation of the substance,¹ although it had apparently previously been obtained by Oldham by hydrolysis of tetraacetylglucose-6-mononitrate.²

¹ Helferich and Klein, Ann. 450, 219 (1926); Helferich, Moog, and Junger, Ber. 58, 877 (1925).

² Oldham, J. Chem. Soc. 127, 2840 (1925).

GUANIDOACETIC ACID (Glycocyamine)



Submitted by E. BRAND and F. C. BRAND.

Checked by C. F. H. ALLEN and JOHN W. GATES, JR.

1. Procedure

(A) *S-Ethylthiourea Hydrobromide*.—A mixture of 150 g. of powdered thiourea (1.97 moles) (Note 1), 250 g. of ethyl bromide (2.29 moles), and 200 cc. of absolute alcohol is placed in a 1-l. round-bottomed flask equipped with an efficient condenser. The mixture is warmed on a water bath (bath temperature 55–65°) for three hours, with occasional shaking. During this time all the thiourea dissolves. The reflux condenser is replaced by one set for downward distillation, and the alcohol and excess ethyl bromide are removed under the vacuum of a water pump. During the distillation, the temperature of the bath is slowly raised to the boiling point (Note 2). The residual oil is poured into a 500-cc. beaker and allowed to crystallize (Note 3). The solid is pulverized and dried in a desiccator (Notes 4 and 5). The yield is 340–360 g. (93–99 per cent of the theoretical amount).

(B) *Guanidoacetic Acid*.—This reaction should be carried out in a well-ventilated hood, as considerable amounts of ethyl mercaptan are evolved. In a 1-l. Erlenmeyer flask is placed 92.5 g. (0.50 mole) of S-ethylthiourea hydrobromide. The flask is immersed in an ice bath, and 252 cc. of 2 *N* sodium hydroxide solution is added. A hot (80 + °) solution of 41 g. of glycine (Org. Syn. Coll. Vol. 1, 1st Ed. (1932), p. 292; 2nd Ed. (1941), p. 298) in 90 cc. of water is added rapidly. When the temperature

reaches 25° (Note 6), the flask is removed from the ice water. After about a half hour crystallization begins; then approximately 100 cc. of ether is added, and the mixture is left in the hood overnight (Note 7). The mixture is then chilled for two hours in an ice bath, the ether layer is decanted, and the solid is filtered with suction. The crystals are washed on the funnel successively with two 20-cc. portions of ice water (Note 8), two 150-cc. portions of 95 per cent alcohol, and two 150-cc. portions of ether. The yield of air-dried guanidoacetic acid is 47–53 g. (80–90 per cent of the theoretical amount). This product is pure enough for most purposes (Note 9); it melts with decomposition at 280–284°.

2. Notes

1. Commercial thiourea is usually sufficiently finely divided so that it may be used directly.
2. The last traces are more quickly removed if the vacuum line is attached directly to the flask.
3. If the product is inoculated, the liquid solidifies at once.
4. The crude product is sufficiently pure for the subsequent reaction. If kept in a cool place in the absence of air, it is stable for several months.
5. This is a general method for preparing *S*-alkylthiourea hydrobromides and hydriodides. The yields are always over 90 per cent. The hydrochlorides are not so readily prepared; it is necessary to determine, by experiment, the optimum conditions for each hydrochloride.
6. The temperature may rise or fall to 25°, depending upon the temperatures of the component solutions.
7. The yield is slightly lower (45 g.) if the mixture is filtered after standing for only three hours.
8. The product is appreciably soluble in water.
9. Further purification of this product may be accomplished by (a) recrystallizing it from hot water (125 cc. per 5 g.), or (b) dissolving it in slightly more than the calculated amount of 2 *N* hydrochloric acid and reprecipitating by adding an equivalent quantity of 2 *N* sodium hydroxide. Analytical values for nitrogen

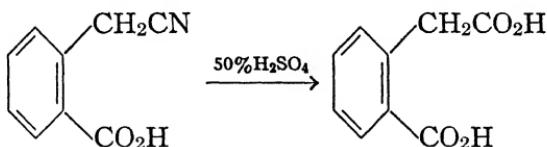
(Dumas) given by the crude and purified products were as follows: Calculated: 35.9 per cent. Found: acid as prepared, 35.4 per cent; once recrystallized, 35.9 per cent; reprecipitated, 35.7 per cent.

3. Methods of Preparation

S-Ethylthiourea has been prepared as the hydrobromide^{1, 2, 3} and hydriodide.^{2, 4} Guanidoacetic acid has previously been made from *S*-ethylthiourea hydriodide.²

HOMOPHTHALIC ACID

(*o*-Toluic Acid, *o*-carboxy-)



Submitted by CHARLES C. PRICE.

Checked by W. E. BACHMANN and RICHARD D. MORIN.

1. Procedure

A MIXTURE of 50 g. of *o*-carboxyphenylacetonitrile (p. 30) and 50 g. of 50% sulfuric acid is placed in a 200-cc. flask. The mixture is heated on a steam bath for ten to twelve hours and is then poured into twice its volume of ice and water. The precipitate is collected on a Büchner funnel and dried in the air. The acid, which weighs 40–42 g. (71–75 per cent of the theoretical amount), may be recrystallized by dissolving it in a liter of boiling water, treating with Norite, filtering the hot solution, and cooling the filtrate in an ice bath. The recovery is 32–35 g. of practically colorless acid (Note 1) which melts at 180–181° (Note 2).

¹ Claus, Ber. 7, 236 (1874).

² Wheeler and Merriam, Am. Chem. J. 29, 483 (1903).

³ Schotte, Priebe, and Roescheisen, Z. physiol. Chem. 174, 119 (1928).

⁴ Claus, Ber. 8, 41 (1875).

2. Notes

1. In one run the checkers used *o*-carboxyphenylacetonitrile which was colored, and it was found necessary to recrystallize the homophthalic acid twice with the aid of Norite. The yield of practically colorless acid was 34.5 g.

2. The melting point depends on the rate of heating. When the capillary tube was placed in the bath at 170° the acid melted at 182–183° with previous softening. When the capillary tube was placed in a bath at room temperature the acid melted at about 174–175°.

3. Methods of Preparation

Homophthalic acid has been prepared from naphthalene via phthalonic acid;¹ from hydrindone by nitrosation, hydrolysis, and hydrogen peroxide oxidation;² from hydrindene by oxidation with chromic and sulfuric acids;³ and from *o*-toluic acid by bromination of the acid chloride followed by treatment with alcohol and sodium cyanide and hydrolysis with 50 per cent sulfuric acid.⁴ Since phthalide has become commercially available, the preparation outlined above, essentially that described by Wislicenus⁵ fifty-six years ago, is by far the simplest and most economical.

¹ Graebe and Trümpy, Ber. **31**, 375 (1898).

² Perkin, Roberts, and Robinson, J. Chem. Soc. **101**, 232 (1912).

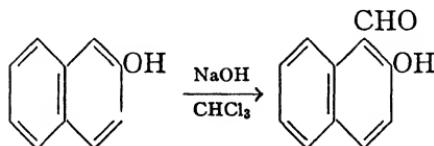
³ Meyer and Vittenet, Compt. rend. **194**, 1250 (1932).

⁴ Price, Lewis, and Meister, J. Am. Chem. Soc. **61**, 2762 (1939).

⁵ Wislicenus, Ann. **233**, 102 (1886).

2-HYDROXY-1-NAPHTHALDEHYDE

(1-Naphthaldehyde, 2-hydroxy-)



Submitted by ALFRED RUSSELL and LUTHER B. LOCKHART.

Checked by W. E. BACHMANN and CHARLES E. MAXWELL.

1. Procedure

IN a 2-l. three-necked, round-bottomed flask (Note 1) fitted with a 40-in. reflux condenser, a mercury-sealed stirrer, and a dropping funnel are placed 100 g. (0.69 mole) of β -naphthol and 300 g. of 95 per cent ethyl alcohol. The stirrer is started, and a solution of 200 g. (5 moles) of sodium hydroxide in 415 g. of water is rapidly added.

The resulting solution is heated to 70–80° on a steam bath, and the dropwise addition of chloroform is started. *After the reaction begins (Note 2), further heating is unnecessary. A total of 131 g. (1.1 moles) of chloroform is added at such a rate that gentle refluxing is maintained (Note 3). Near the end of the addition the sodium salt of the phenolic aldehyde separates. Stirring is continued for one hour after all the chloroform has been added.

The alcohol and excess chloroform are removed by distillation from a steam bath. Hydrochloric acid (sp. gr. 1.18) is added dropwise to the residue, with good stirring, until the contents of the flask are acid to Congo red paper (Note 4). The dark oil which separates is mixed with a considerable amount of sodium chloride. Sufficient water to dissolve the salt is added, and the oil is separated and washed several times with hot water. By distillation of the oil under reduced pressure there is obtained 87.5–93.7 g. of a slightly colored distillate which boils at 163–166° at 8 mm. (Note 5) and which solidifies on cooling. Recrystallization

of the solid from 75 cc. of alcohol yields 45.2–57.5 g. (38–48 per cent of the theoretical amount) of pure 2-hydroxy-1-naphthaldehyde, melting at 79–80°.

2. Notes

1. The submitters employed a 5-l. flask for a run four times this size. They obtained the same percentage yield of product.
2. The beginning of the reaction is indicated by the formation of a deep blue color.
3. The chloroform is added over a period of one to one and one-half hours.
4. About 175 cc. of hydrochloric acid is required to neutralize the excess sodium hydroxide and to liberate the phenolic aldehyde from its sodium salt.
5. The boiling range of the aldehyde is 177–180° at 20 mm. The lower pressure is preferable to avoid decomposition. The checkers found a boiling point of 139–142° at 4 mm. The color of the distillate varies in different runs; it may be green, pink, or amber.

3. Methods of Preparation

2-Hydroxy-1-naphthaldehyde has been prepared from β -naphthol, zinc chloride, and hydrogen cyanide;¹ from β -naphthol, zinc cyanide, and anhydrous hydrogen chloride;² and from β -naphthol, chloroform, and sodium hydroxide (Reimer-Tiemann reaction).³

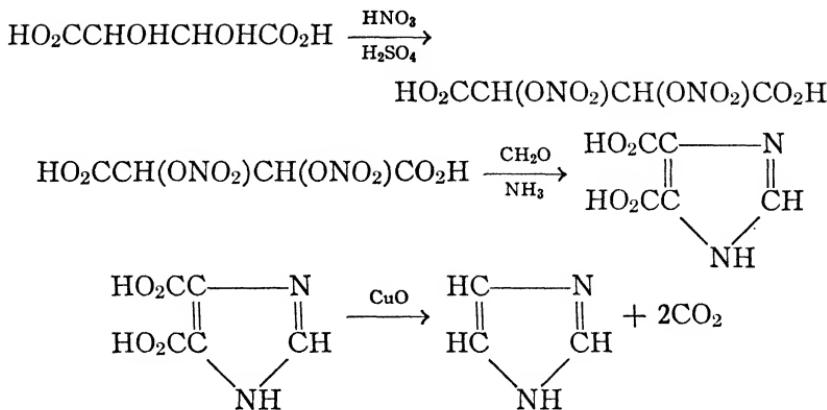
¹ Gattermann and von Horlacher, Ber. **32**, 285 (1899).

² Adams and Levine, J. Am. Chem. Soc. **45**, 2373 (1923).

³ Fosse, Bull. soc. chim. (3) **25**, 373 (1901).

IMIDAZOLE

(1,3-Diazole; Glyoxaline)



Submitted by H. R. SNYDER, R. G. HANDRICK, and L. A. BROOKS.

Checked by C. F. H. ALLEN, C. J. KIBLER, and JAMES VAN ALLAN.

1. Procedure

IN a 2-l. three-necked, round-bottomed flask fitted with a thermometer, mechanical stirrer, and 1-l. dropping funnel is placed 200 g. (1.33 moles) of powdered *d*-tartaric acid (Note 1). To this are added, successively, 432 cc. of nitric acid (sp. gr. 1.42) and 432 cc. of fuming nitric acid (sp. gr. 1.50). The mixture is stirred until the tartaric acid is all, or nearly all, in solution (five to ten minutes) (Note 2). Then 800 cc. of concentrated sulfuric acid (sp. gr. 1.84) is slowly added from the dropping funnel. As soon as the temperature of the reaction mixture reaches 38°, the flask is surrounded by a vessel of ice water, and the rate of addition of acid is regulated so that the temperature is maintained at 38–43° (Note 3). Near the end of the addition (about fifteen minutes), tartaric acid dinitrate sometimes begins to crystallize. After all the sulfuric acid has been added the mixture is allowed to stand in a cool (20–25°) place for three hours.

The crystalline mass is broken up with a glass rod and collected on a glass filter cloth (Note 4) in an 18-cm. Büchner funnel.

The resulting cake is pressed nearly dry by means of a large flat glass stopper or the bottom of a 125-cc. Erlenmeyer flask. After most of the mother liquor has been removed (Note 5), the solid is transferred in portions to a 4-l. beaker containing about 3 l. of *finely cracked* ice. The ice is stirred to effect solution of each portion of the solid as it is added; a wooden stirring rod with a flat end is advisable. Not more than ten minutes should be required.

The cold solution is poured *immediately* into a previously assembled apparatus, consisting of a 5-l. three-necked flask, immersed in a 20-in. tub of ice-salt mixture (Note 6), and provided with a stirrer, dropping funnel, and thermometer for reading low temperatures. The solution is neutralized by the addition of 600–700 cc. of concentrated ammonium hydroxide (sp. gr. 0.90) at such a rate that the temperature *never* exceeds -5° (Note 7); the tip of the dropping funnel should be placed directly over the vortex created by the stirrer. After 500 cc. of ammonium hydroxide has been added, the solution is tested with Congo red paper at intervals corresponding to the addition of 50 cc. of ammonium hydroxide; three to four hours is required for the neutralization. An additional 100 cc. of ammonium hydroxide is then added.

While the neutralization is in progress, a solution of hexamethylenetetramine (Note 8) is prepared by the cautious addition of 520 cc. of formalin (sp. gr. 1.08; approximately 7 moles) to 500 cc. of ammonium hydroxide (sp. gr. 0.90; approximately 7.5 moles). The temperature must be maintained below 20° by external cooling with ice water. The solution is finally chilled to 0° and added dropwise to the cold ammoniacal solution of tartaric acid dinitrate; the temperature should not exceed 2° . The addition requires half an hour. Stirring is then discontinued, and the mixture is allowed to stand overnight. During this period the cooling bath and the reaction mixture come to room temperature.

The solution is now filtered, and 100 cc. of alcohol is added to the filtrate, which is then acidified (hood) to Congo red paper by the slow (thirty minutes) addition of about 400 cc. of concentrated hydrochloric acid (sp. gr. 1.19). The acidified mixture is cooled in an icebox for four to five hours, and the imidazole-4,5-

dicarboxylic acid is collected on an 18-cm. Büchner funnel. The solid is transferred to a 1-l. beaker, stirred with 400–500 cc. of water, and again filtered. It is washed on the funnel successively with three 150-cc. portions of water, two 75-cc. portions of methyl alcohol, and finally with 75 cc. of ether. After drying in the air, it weighs 90–100 g. (43–48 per cent of the theoretical amount) and melts with decomposition at about 280°.

The imidazole-4,5-dicarboxylic acid is divided into two portions. Each portion is intimately mixed with about 0.5 g. of copper-chromium oxide catalyst (Org. Syn. 19, 31) or powdered copper oxide (Note 9), and the resulting mixture is transferred to a 250-cc. Claisen flask having a modified side arm (p. 11); the receiving flask is loosely placed over the side arm. The flask is heated gently with a free flame. After a small fore-run at 95–100°, the temperature rises sharply to 260° (Note 10), and the imidazole distils at 262–264°. The product is purified by dissolving it in 60–70 cc. of benzene, boiling the solution for a few minutes with 2–3 g. of decolorizing carbon (Note 11), filtering the mixture through a preheated Büchner funnel, and cooling the filtrate to 10° for two hours. The yield is 13–14.5 g. (68–76 per cent of the theoretical amount) of a pure white product, m.p. 88–90° (Note 12).

2. Notes

1. The submitters used U.S.P. tartaric acid. The checkers used the Eastman Kodak Company acid, m.p. 169–171°.
2. It is possible to carry out the preparation without mechanical stirring, merely using a single-necked flask and shaking by hand. Temperature control is not so satisfactory under these conditions.
3. At lower temperatures tartaric acid dinitrate separates during the addition of the sulfuric acid. Under these conditions, it forms very fine crystals that are not easily filtered.
4. Vinyon fabric serves equally well. If a filter cloth is not available, a layer of glass wool is prepared on the funnel; the mixed wool and solid are then added to the cracked ice.

5. A fairly dry cake is obtained in about forty-five minutes. Since the substance decomposes in the air, it is advisable not to leave it for a longer period.

6. Efficient cooling is extremely important; a small ice bath will not suffice.

7. The decomposition temperature is about 0°. A centrifugal-type stirrer is advisable.

8. No product was obtained when solid hexamethylene-tetramine was substituted at this point.

9. Copper oxide gives a slightly lower yield.

10. If an ordinary 250-cc. distilling flask is used, the fraction boiling from 200° to 270° is collected as crude imidazole. The fore-run contains about 1 g. of imidazole, which can be recovered by boiling this fraction of the distillate with benzene, until the water is removed, and then evaporating to crystallization.

11. If a flask and fractionating column are used, the crude product is white; otherwise it is colored.

12. The benzene filtrate from the recrystallization contains about 0.5 g. of imidazole.

3. Methods of Preparation

Imidazole has been prepared from glyoxal and ammonia, with¹ or without² the addition of formaldehyde; from imidazolthione-2 and nitric acid;³ and by decarboxylation of imidazole-4,5-dicarboxylic acid.^{4, 5, 6} The procedure described is essentially that of Fargher and Pyman.⁶

¹ Wallach, Ber. **15**, 645 (1882).

² Behrend and Schmitz, Ann. **277**, 338 (1893).

³ Marckwald, Ber. **25**, 2361. (1892).

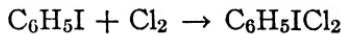
⁴ Maquenne, Ann. chim. (6) **24**, 525 (1891).

⁵ Dedichen, Ber. **39**, 1835 (1906).

⁶ Fargher and Pyman, J. Chem. Soc. **115**, 227 (1919).

IODOBENZENE DICHLORIDE

(Benzene, iodo-, dichloride-)



Submitted by H. J. LUCAS and E. R. KENNEDY.

Checked by JOHN R. JOHNSON and M. W. FORMO.

1. Procedure

IN a 1-l. three-necked flask, protected from the light and equipped with a mechanical stirrer, an inlet tube for the introduction of chlorine (Note 1), and an exit tube carrying a calcium chloride drying tube, are placed 150 cc. of dry chloroform (Note 2) and 102 g. (0.5 mole) of iodobenzene (Org. Syn. 19, 55). The flask is cooled in an ice-salt mixture, and dry chlorine (Note 3) is introduced, as rapidly as the solution will absorb it, until an excess is present (usually about three hours is required). The yellow, crystalline iodobenzene dichloride is filtered with suction, washed sparingly with chloroform, and dried in the air on filter paper. The yield is 120–134 g. (87–94 per cent of the theoretical amount) (Notes 4 and 5). The product is quite pure and may be used directly for the preparation of iodosobenzene and iodoxybenzene. Since iodobenzene dichloride decomposes slowly on standing, it should not be stored indefinitely.

2. Notes

1. The delivery tube should be at least 10 mm. in diameter and should terminate about 5 mm. above the surface of the liquid.
2. Chloroform was dried and rendered free of alcohol by allowing it to stand over anhydrous calcium chloride for twenty-four hours. It was then decanted through a filter and distilled through dry apparatus. The initial low-boiling fraction was rejected.
3. Chlorine was dried by passing it through at least two wash bottles containing sulfuric acid. Spray was removed by passing

the gas through a plug of glass wool. The yields are reduced appreciably if the reactants are not dry.

4. In some runs an additional quantity of the product may be obtained by evaporating the chloroform filtrate to a small volume under reduced pressure. The solvent must not be evaporated completely if a pure product is desired.

5. The submitters report that the three isomeric iidotoluene dichlorides may be prepared in good yields by a similar procedure, but in these cases the chloroform solution must be concentrated by evaporation under reduced pressure (Note 4), since the tolyl homologs are more soluble in chloroform.

3. Methods of Preparation

Iodobenzene dichloride has always been *prepared* by direct combination of iodobenzene and chlorine in the presence of chloroform.¹

IODOSOBENZENE

(Benzene, iodoso-)



Submitted by H. J. LUCAS, E. R. KENNEDY, and M. W. FORMO.
Checked by LEE IRVIN SMITH, R. T. ARNOLD, and R. A. MATTHEWS.

1. Procedure

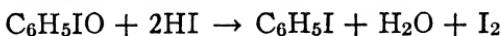
IN a large mortar chilled in an ice bath are placed 55 g. (0.2 mole) of iodobenzene dichloride (p. 69), 50 g. of anhydrous sodium carbonate, and 100 g. of finely crushed ice. The mixture is ground thoroughly (Note 1) until all the ice has melted and a thick paste results. To this suspension 140 cc. of 5 N sodium hydroxide is added, in 20-cc. portions, with repeated trituration after each addition. Finally, 100 cc. of water is added to render the mixture more fluid and the material is allowed to stand overnight. The product is collected with suction, pressed thoroughly on the filter, transferred to a beaker, and washed thoroughly with

¹ Willgerodt, J. prakt. Chem. (2) 33, 155 (1886).

300 cc. of water (Note 2). The material is filtered with suction, washed again in a beaker with 300 cc. of water, collected with suction, and washed with about 250 cc. of water on the filter. After thorough drying in the air, the product is stirred to a thin mush with a little chloroform (Note 3), freed of solvent by suction, and spread on filter paper to dry in the air. The yield is 26–27 g. (60–62 per cent of the theoretical amount) of a product having a purity of about 99 per cent, as determined by titration (Notes 4 and 5).

2. Notes

1. The solid forms a caked mass, which is disintegrated by trituration.
2. The filtrate contains some diphenyliodonium salts, which may be recovered in the form of the sparingly soluble iodide by the addition of potassium iodide (p. 52). Usually 7–9 g. of diphenyliodonium iodide is obtained.
3. The chloroform removes iodobenzene, which may be recovered.
4. The following procedure is used in the analysis of iodoso and iodoxy compounds. In a 200-cc. iodine flask are placed 100 cc. of water, 10 cc. of 6 *N* sulfuric acid, 2 g. of iodate-free potassium iodide, 10 cc. of chloroform, and finally the sample, about 0.25 g. The flask is shaken for fifteen minutes (or longer, if the reaction is not complete), and then the mixture is titrated with 0.1 *N* sodium thiosulfate. If the sample is pure the change of color in the chloroform layer may be taken as the end point, but if impurities are present starch must be used, for the impurities impart a brownish color to the chloroform. This solvent is desirable, as it facilitates the reaction with potassium iodide by dissolving the reaction products. Iodosobenzene may be differentiated from iodoxybenzene, for the former reduces iodide ion in a saturated sodium borate solution, whereas the latter does not.¹ The reactions involved are:



¹ Masson, Race, and Pounder, J. Chem. Soc. 1935, 1678.

5. For use in the preparation of iodoxybenzene by the disproportionation method (p. 72) it is superfluous to dry the crude product and to wash it with chloroform to remove iodobenzene. The crude wet iodosobenzene may also be used directly for the preparation of diphenyliodonium iodide (p. 52), but it is desirable to assay the wet product by titration to determine the quantity of iodoxybenzene needed.

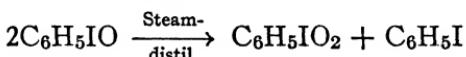
3. Methods of Preparation

Iodosobenzene has been prepared by the action of aqueous sodium or potassium hydroxide upon iodobenzene dichloride;² and by repeated additions of water to iodobenzene dichloride.³

IODOXYBENZENE

(Benzene, iodoxy-)

(A) Disproportionation of Iodosobenzene



Submitted by H. J. LUCAS and E. R. KENNEDY.
Checked by JOHN R. JOHNSON and M. W. FORMO.

1. Procedure

IN a 5-l. flask (Note 1), 110 g. (0.5 mole) of iodosobenzene (p. 70) is made into a thin paste with water, and the mixture is rapidly steam-distilled (Note 2) until almost all the iodobenzene (Note 3) is removed. The distillation should not be continued any longer than necessary, and the contents of the flask should be cooled at once. The white solid is filtered with suction and dried in the air at room temperature. It is then washed with chloroform, again dried, and the resulting cake is ground lightly

² Willgerodt, Ber. **25**, 3495 (1892); **26**, 357, 1807 (1893); Askenasy and Meyer, Ber. **26**, 1356 (1893); Hartmann and Meyer, Ber. **27**, 505 (1894).

³ Willgerodt, Ber. **26**, 357 (1893); Ortoleva, Chem. Zentr. **1900**, I, 722.

in a mortar to facilitate removal of moisture in a final drying. The yield is 54–56 g. (92–95 per cent of the theoretical amount). The product has a purity of about 99 per cent, as determined by iodimetry (Note 4). The solid may be crystallized from hot water (Note 5).

2. Notes

1. Because of a tendency to froth, a large flask should be used.
2. Direct heating must be avoided, as the solid reactant and product may decompose with explosive violence on heating, especially when dry.
3. The recovered iodobenzene is quite pure and may be used for the preparation of iodobenzene dichloride. The recovery is about 46 g. (90 per cent of the theoretical amount).
4. The iodimetric method described under iodosobenzene (p. 71) is applicable here. The main impurity in the iodoxybenzene is iodosobenzene.
5. The solubility of iodoxybenzene, per liter of water, is 2.8 g. at 12°, and about 12 g. at 100°.

(B) Hypochlorite Oxidation of Iodobenzene Dichloride



Submitted by M. W. FORMO and JOHN R. JOHNSON.

Checked by LEE IRVIN SMITH, R. T. ARNOLD, and LOUIS E. DEMYTT.

1. Procedure

IN a 2-l. round-bottomed flask equipped with an efficient mechanical stirrer (Note 1) are placed 110 g. (0.4 mole) of freshly prepared, pulverized iodobenzene dichloride (p. 69) (Note 2), 1.0 mole of sodium hypochlorite solution (Note 3), and 2 cc. of glacial acetic acid. The vigorously stirred mixture is heated on a water bath maintained at 65–75°. After ten to fifteen minutes the heated mixture becomes frothy and the yellow color of iodobenzene dichloride is displaced by the white color of iodoxybenzene. The stirring is stopped after one hour, and the flask is cooled in an ice bath. The product is filtered with suction,

pressed with a glass stopper, and transferred to an 800-cc. beaker. The material is stirred thoroughly with 300 cc. of water, filtered with suction, washed on the filter with 100 cc. of water, pressed, and dried in the air. The crude product weighs 85–89 g. (90–94 per cent of the theoretical amount) and has a purity, as determined iodimetrically, of 97–99 per cent (Note 4). The air-dried material may be washed with 50–60 cc. of chloroform, air-dried, and finally dried in a vacuum desiccator. This product weighs 82–87 g. (87–92 per cent of the theoretical amount) and has a purity of 99.0–99.9 per cent as determined by iodimetry (Note 5).

2. Notes

1. The Hershberg stirrer (Org. Syn. 17, 31) is well suited for stirring the pasty suspension.
2. Any lumps of iodobenzene dichloride should be broken up by pressing with a spatula; otherwise the reaction may be incomplete.
3. Stabilized hypochlorite solutions, commercially available, are satisfactory. The submitters used 1.15 l. of "Clorox" solution, containing 5.25 per cent sodium hypochlorite by weight.
4. The iodimetric method as described under iodosobenzene (p. 71) is applicable here. The crude product is satisfactory for the preparation of diphenyliodonium iodide (p. 52).
5. The checkers obtained the yields claimed, but the purity of the product was 90 per cent before, and 95.7 per cent after, washing with chloroform.

3. Methods of Preparation

Iodoxybenzene has been prepared by oxidizing iodobenzene with Caro's acid;^{1, 2} by treating iodobenzene with hypochlorous acid or with aqueous sodium hydroxide and bromine;³ by action of chlorine upon iodobenzene dissolved in pyridine;⁴ by oxidation

¹ Bamberger and Hill, Ber. **33**, 534 (1900).

² Masson, Race, and Pounder, J. Chem. Soc. **1935**, 1678.

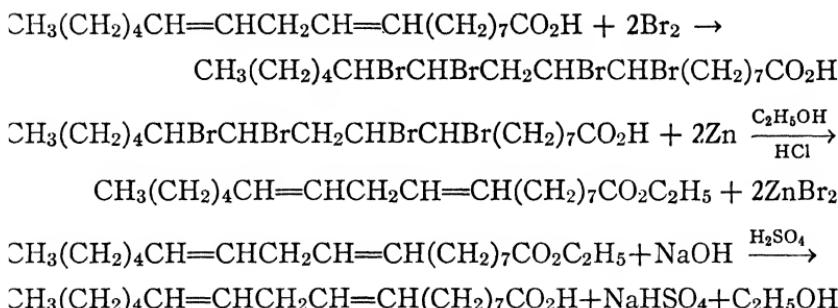
³ Willgerodt, Ber. **29**, 1571, 1572 (1896).

⁴ Ortoleva, Chem. Zentr. **1900**, I, 723.

of iodosobenzene with hypochlorous acid or bleaching powder;⁵ by heating iodosobenzene;⁶ by steam distillation of iodosobenzene;⁷ by heating iodobenzene dichloride with aqueous sodium hypochlorite containing some acetic acid;⁸ and by oxidation of iodobenzene with concentrated chloric acid solution.⁹

LINOLEIC ACID

(Linolic Acid)



Submitted by J. W. McCUTCHEON.

Checked by R. L. SHRINER and S. P. ROWLAND.

1. Procedure

(A) *Fatty Acids.*—In a 1-l. Erlenmeyer flask are placed 250 cc. of dynamite-grade glycerin (Note 1) and 40 g. (0.71 mole) of potassium hydroxide. The mixture is heated to 120–140° and is shaken by hand until the alkali is dissolved. To the hot solution there is added, in one portion (Note 2), 110 cc. (100 g., 0.11 mole) of sunflower-seed oil (Notes 3 and 4) which has been preheated to 110–115°. The hot solution is swirled vigorously until saponification is complete (Note 5). This is indicated by the formation of a

⁵ Willgerodt, Ber. **29**, 1568, 1569 (1896).

⁶ Willgerodt, Ber. **25**, 3500 (1892); **26**, 1806 (1893); Askenasy and Meyer, Ber. **26**, 1356 (1893).

⁷ Willgerodt, Ber. **26**, 358, 1307 (1893).

⁸ Willgerodt and Wiegand, Ber. **42**, 3765 (1909).

⁹ Datta and Choudhury, J. Am. Chem. Soc. **38**, 1085 (1916).

permanent lather. After the mixture has cooled somewhat, 150 cc. of sulfuric acid (25 per cent by volume) is added cautiously (Note 6) while the flask is swirled. Then 200 cc. of hot water is added, and, if necessary, the mixture is heated until the layer of fatty acid is clear. The water layer is removed, the acid layer is washed with two 500-cc. portions of hot water, and then it is filtered with the aid of suction through a large Hirsch funnel which is heated by a steam or hot water jacket. The acids (90–95 g.) (Note 7) are dried thoroughly by heating them rapidly to 130°, with stirring.

(B) *Tetrabromostearic Acid*.—In a 4-l. beaker equipped with a mechanical stirrer the above fatty acids are dissolved in 2 l. of petroleum ether (Note 8), and the solution is chilled to 0–10°. After twenty to twenty-five minutes, the solution deposits about 10 g. of solid saturated fatty acids, which are removed by rapid filtration with gentle suction. The filtrate is transferred to the 4-l. beaker and cooled to 0–10°. Then, with stirring, 30.7 cc. (90 g., 0.56 mole) of bromine (Note 9) is slowly introduced from a dropping funnel (Note 10). The bromine is added at such a rate that the temperature remains between 10° and 15°; about twenty minutes is usually required. Tetrabromostearic acid begins to separate toward the end of the addition. The solution, which should contain a slight excess of bromine (reddish color), is allowed to remain in the ice bath for fifteen to twenty minutes (Note 11). The precipitate settles rapidly, and a large portion of the liquid is removed by decantation, after which the precipitate is finally collected with suction on a 12.5-cm. Büchner funnel and is washed with 200 cc. of petroleum ether. The solid is then thoroughly stirred with 300 cc. of petroleum ether (Note 12) in a 600-cc. beaker and is filtered as before. The gray-white tetrabromide, after drying at 50°, is transferred to a 2-l. beaker and dissolved in 90–100 cc. of hot ethylene dichloride (Note 13). The solution is filtered through filter paper and allowed to crystallize at room temperature. The solid is removed by filtration and is washed on the funnel with 200 cc. of fresh petroleum ether. The tetrabromide is transferred to a *glass plate* and is worked to a powder (Note 14) with a spatula. The needle-shaped crystals

are snow-white, with a silvery sheen, and have a melting point of 114.7–115.2°. The yield (Note 15) is 35–40 g. (32–36 per cent of the theoretical amount) (Note 16). The product should be stored in brown screw-top bottles and kept away from sunlight.

(C) *Ethyl Linoleate*.—In a 300-cc. Erlenmeyer flask are placed 26–30 g. of recrystallized tetrabromostearic acid, 85 cc. of absolute ethyl alcohol, and 30 g. of granulated zinc (20 mesh). This mixture is warmed gently until the debromination reaction begins. Since the reaction is exothermic, it is usually necessary to moderate it from time to time by dipping the flask into a basin of cold water. The vigorous reaction subsides in about five minutes, after which the flask is fitted with a reflux condenser and the mixture is refluxed for thirty minutes. In order to esterify the linoleic acid, 10 cc. of a 4 *N* solution of hydrochloric acid in ethyl alcohol (Note 17) is poured into the refluxing mixture through the top of the condenser, and successive 5-cc. portions are then added every thirty minutes for two hours. At the end of this time the solution is removed from the unchanged zinc by decantation into another flask. The zinc is washed with 15 cc. of absolute alcohol to complete the transfer of the solution. A 10-cc. portion of 4 *N* alcoholic hydrochloric acid is added and the solution is refluxed for an hour, with addition of a second 10-cc. portion of alcoholic acid after thirty minutes. The mixture is poured into 300 cc. of hot, saturated brine solution in a 500-cc. separatory funnel, and the crude ester is allowed to settle for ten to twenty minutes. The brine layer is removed, and the ester is washed (Note 18) at room temperature with 300 cc. of 0.5 per cent sodium carbonate solution. The rather stable emulsion is broken by centrifuging the solution, in 100-cc. tubes, for five minutes at 3300 r.p.m. The ester and any remaining emulsion are washed with 80 cc. of warm water, and the emulsion is again broken by centrifuging. Washing is continued (Note 19) until the wash water is neutral to methyl orange. The neutral ester is then transferred to a 50-cc. distilling flask and is distilled under reduced pressure; boiling point, 175°/2.5 mm., 193°/6 mm. The product is water-white (Note 20), gives a negative Beilstein test, has an iodine value (Wijs, thirty-minute exposure) of 162.3–162.5, an n_D^{48} of 1.4489,

and a true specific gravity of 0.8846 at 15.5/4°. The yield (Note 15) is 12–15 g.

(D) *Linoleic Acid*.—The ester is dissolved in 200 cc. of a 5 per cent alcoholic (Note 21) solution of sodium hydroxide in a 400-cc. beaker and is allowed to saponify overnight at room temperature. The resulting jelly is dissolved in 200 cc. of warm water, and a slow stream of carbon dioxide is introduced, beneath the surface of the liquid, while it is acidified with 50 cc. of dilute sulfuric acid (1:1 by volume). The stream of carbon dioxide is maintained throughout the subsequent operations. The linoleic acid rises to the surface as a clear layer. The water layer is siphoned off; the acid is washed once with hot water and then dried over anhydrous sodium sulfate and preserved under carbon dioxide. The yield is 10–12 g. of material having a melting point of –8° to –9° C. (Note 22).

2. Notes

1. Dynamite-grade glycerin is specified, because of its high glycerol content (99 plus per cent). Water interferes with the ease of saponification.
2. The oil must not be allowed to run down the side of the flask, as this interferes with complete saponification.
3. The following oils are recommended in decreasing order of preference, the bracketed numbers indicating the approximate linoleic acid content: sunflower-seed oil (60), poppy-seed oil (60), cotton-seed oil (45).
4. The sample used must have a negative hexabromide test, indicating the absence of acids more highly unsaturated than linoleic. The test is carried out as follows: 2 cc. of the oil and 25 cc. of a 4:1 ethyl ether-glacial acetic acid mixture are chilled to 0° for fifteen to twenty minutes; the mixture is filtered if it is not clear. To this solution is added sufficient bromine to give a deep red color, and the whole is allowed to stand for fifteen minutes. The absence of a precipitate constitutes a negative test.
5. Usually four to six minutes of vigorous swirling is sufficient, but it may be necessary to reheat the mixture to 150° if difficulty is encountered. Saponification, once started, proceeds to com-

pletion within a few seconds. The emulsion thickens to a viscous paste which is transformed into a clear limpid solution on continued swirling.

6. By adding the acid to the *hot* solution, with vigorous agitation, delay in clearing the fatty acid layer is avoided.

7. When large quantities of the fatty acids are desired, the following method is more economical: In a 5-l. round-bottomed flask, fitted with a mechanical stirrer and a reflux condenser, are placed 1.5 l. of methyl alcohol and 350 g. of potassium hydroxide. After solution is complete, 1.1 l. (1 kg.) of cotton-seed oil is added. The solution is stirred and refluxed for one to two hours, and then the methyl alcohol is removed by distillation. To the residue are added 1 l. of water and (slowly) 1.5 l. of cold 20 per cent sulfuric acid. The fatty acid layer is separated from the water layer, washed with two 1.5-l. portions of hot water, and then filtered with the aid of a hot water funnel. The acids are dried as described above. The yield is 950–975 g. of crude acids.

8. The petroleum ether used throughout had a boiling range of 40–60°.

9. The weight of bromine is independent of the amount (per cent) of linoleic acid in the sample, but it varies with the iodine value.¹ For the purpose of this preparation, the amount of bromine (grams) may be calculated as 0.7 times the iodine value of the oil. This allows an excess of 10–11 per cent.

10. The tip of the dropping funnel should be just above the fatty acid solution.

11. Tetrabromostearic acid has a decided tendency to form a supersaturated solution in petroleum ether.

12. The solubility of the tetrabromide² is about 2–3 g. per l. of petroleum ether at room temperature, hence there is little danger of losing appreciable quantities by solution during the washing.

13. As an alternative but less satisfactory method of purifica-

¹ Official and Tentative Methods of the American Oil Chemists Society, revised to Jan. 1, 1941, p. 31, Gillette Pub. Co., 330 S. Wells St., Chicago.

² McCutcheon, Can. J. Research B16, 158–175 (1938).

tion, the crude tetrabromide may be dissolved in 800 cc. of ethyl ether, filtered, and reprecipitated by stirring the solution into 800 cc. of petroleum ether. This solution is cooled below 20° and allowed to stand overnight. Ninety per cent of the precipitate will be deposited in two hours. The solid is removed by filtration and is washed on the funnel as described above.

14. The ease with which the product dries and powders is an indication of its purity. Usually the material falls apart to a fine white powder at the mere touch of the spatula. A glass spatula should be used in the transfer of the crude material before the recrystallization.

15. These figures are based on the use of sunflower-seed oil containing 57 per cent linoleic acid. With other oils, the yield will be proportionally larger or smaller, depending on the analysis of the oil. Approximate values for three oils may be calculated from the values given in Note 3 above. The yield from cotton-seed oil is 26-30 g. The checkers have brominated about nine times the amounts stated in these directions and have obtained proportionate yields.

16. Two isomers, a solid and a liquid, are formed during the bromination.

17. The 4 *N* alcoholic-hydrochloric acid is prepared by passing dry hydrogen chloride gas into slightly warmed absolute ethyl alcohol until the calculated increase in weight is obtained.

18. The ester contains about 0.5 per cent of free fatty acid, and for some purposes this is not objectionable, particularly if the acid itself is desired. It is recommended, therefore, that this step be omitted where possible since the yields, particularly from the small batches, may be as low as 80 per cent of the crude ester used. In the absence of an alkaline wash, centrifuging is not necessary, as water alone causes no emulsions to form.

19. Usually three washings are sufficient.

20. A small amount of decolorizing carbon may be added before distillation, but it is usually unnecessary and is to be avoided if possible, for it is likely to cause priming in the still.

21. Ordinary 95 per cent denatured alcohol is satisfactory here.

22. The ester is much more stable toward oxidation than the acid; it is recommended that the material be stored as the ester, and that the acid be prepared only for immediate use. The acid oxidizes to some extent under the best of conditions and, unlike the ester, cannot be distilled without some decomposition. It is for this reason that the constants are determined on the ester rather than on the acid.

3. Methods of Preparation

Ethyl linoleate is prepared by debromination of the tetrabromide by action of zinc, or nascent hydrogen from zinc and glacial acetic acid;³ by zinc and alcoholic-hydrochloric acid;^{2, 4} and by zinc and alcoholic-sulfuric acid.⁵ The pure acid can be obtained by saponification of the ester, and directly by action of zinc and pyridine (quinoline, aniline, piperidine) on tetrabromo-stearic acid.⁶

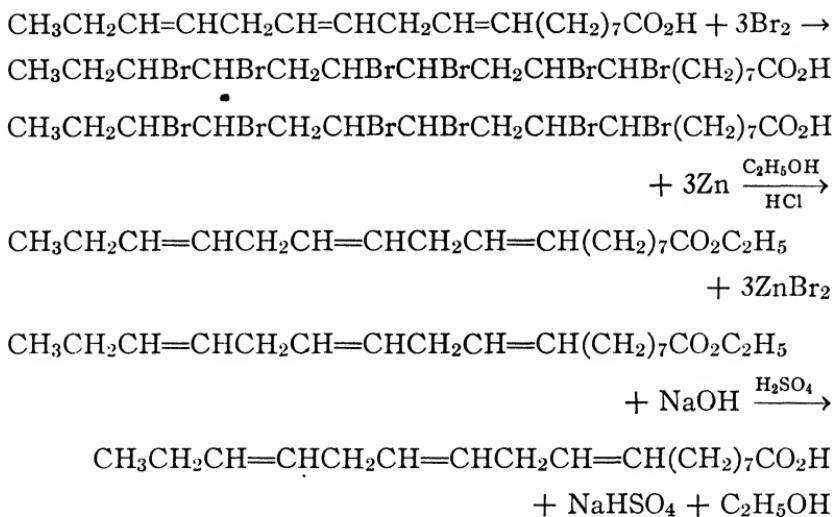
³ Erdmann and Bedford, Ber. **42**, 1324 (1909); Erdmann, Bedford, and Raspe, Ber. **42**, 1334 (1909).

⁴ Rollett, Z. physiol. Chem. **63**, 410-421 (1909).

⁵ Kimura, Fettchem. Umschau **4**, 78 (1935).

⁶ Kaufmann and Mestern, Ber. **69**, 2684 (1936).

LINOLENIC ACID



Submitted by J. W. McCUTCHEON.

Checked by R. L. SHRINER and S. P. ROWLAND.

1. Procedure

(A) *Fatty Acids.*—The procedure outlined for linoleic acid (p. 75) is followed, omitting Notes 3 and 4. Linseed oil is used as the raw material.

(B) *Hexabromostearic Acid.*—In a 4-l. beaker equipped with a mechanical stirrer (Note 1), 90 to 95 g. of the fatty acids is dissolved in 2.5 l. of ethyl ether, and the solution is chilled to 0–10°. Then, with stirring, 35 cc. of bromine (Notes 2 and 3) is introduced slowly, from a dropping funnel (Note 4), at such a rate that the temperature does not exceed 20°; about fifty minutes is usually required. The solution, which must contain an excess of bromine (deep red color), is allowed to stand in an ice bath at 0–10° overnight. The excess bromine is removed by addition of a small amount of amyrene, and then the white precipitate is collected with suction on a 12.5-cm. Büchner funnel and is washed with 200 cc. of ethyl ether. The hexabromide is

thoroughly stirred with 300 cc. of ethyl ether in a 600-cc. beaker and is filtered as before. The yield is 20–22 g. of gray-white hexabromostearic acid (Note 5). It is recommended that 100 g. of the crude hexabromide (Note 6) be accumulated before proceeding to the next step.

In a 1-l. beaker 100 g. of crude hexabromostearic acid is heated to 70–80° with 600 cc. of dioxane (Note 7). The mixture is filtered, and the filtrate is set aside at 15–20° for several hours or preferably overnight. The precipitate is collected on a Büchner funnel with gentle suction and is washed thoroughly on the funnel with several 300-cc. portions of ethyl ether. The hexabromide is then transferred to a glass plate and spread out with a glass spatula to dry in the air. The fine snow-white crystals weigh 80 g. and melt at 181.5–181.9° (Note 8).

(C) *Ethyl Linolenate*.—In a 1-l. Erlenmeyer flask 80 g. of the pure hexabromide is dissolved in 190 cc. of absolute ethyl alcohol, and 40 g. of granulated zinc (20 mesh) is added. The mixture is refluxed for one hour, at the end of which time the solution should be clear. About 10 g. of zinc dust is added, refluxing is continued for a short time, and then 10 cc. of 4 *N* ethyl alcohol-hydrochloric acid (p. 80) is added. Refluxing is continued for six hours, and during this time 5 cc. of the alcoholic hydrochloric acid is added every thirty minutes. At the end of six hours, the solution is removed from the unchanged zinc by decantation into another flask, and the zinc is washed with 15 cc. of absolute alcohol to complete the transfer of the solution. A 10-cc. portion of alcoholic hydrochloric acid is added, and the solution is refluxed for a period of three hours, with addition of 5-cc. portions of alcoholic hydrochloric acid at half-hour intervals. The mixture is poured into 500 cc. of hot saturated brine solution in a 1-l. separatory funnel, and the crude ester is allowed to settle for ten to twenty minutes. The brine is removed, and the ester is washed (Note 9) at room temperature with 500 cc. of 0.5 per cent sodium carbonate solution. The rather stable emulsion is broken by centrifuging the mixture for five minutes at 3300 r.p.m. The ester and any remaining emulsion are washed with 150 cc. of warm water, and the emulsion is broken by centrifuging. Wash-

ing (Note 10) is continued until the wash water is neutral to methyl orange. The neutral ester is distilled under reduced pressure. It boils at $174^{\circ}/2.5$ mm. and $198^{\circ}/6.5$ mm.

(D) *Linolenic Acid*.—The ester is dissolved in 400 cc. of a 5 per cent alcoholic solution of sodium hydroxide in a 1-l. beaker, and the solution is allowed to stand overnight at room temperature. The resulting jelly is dissolved in 400 cc. of warm water, and a slow stream of carbon dioxide is introduced beneath the surface of the liquid while it is acidified with 50 cc. of dilute sulfuric acid (1:1 by volume). The stream of carbon dioxide is maintained throughout the subsequent operations. The linolenic acid rises to the surface as a clear layer, which is washed once with hot water. The acid is dried over anhydrous sodium sulfate and is preserved under carbon dioxide. The yield of acid is 22–24 g., and the product has a melting point of -17° to -16° (Note 11).

2. Notes

1. In order to guard against fire hazard it is advisable to use hand stirring when proper safety equipment is not available.
2. Care must be observed that the stopcock does not slip out of place.
3. The weight of bromine is independent of the amount (per cent) of linolenic acid in the sample, but it varies with the iodine value. For the purposes of this experiment the amount of bromine (grams) may be calculated as 0.7 times the iodine value of the oil. This allows an excess of 10–11 per cent.
4. The tip of the dropping funnel should be just above the fatty acid solution in order to avoid plugging the exit.
5. The yield is based on a linseed oil containing approximately 45 per cent of linolenic acid. Because of the formation of stereoisomers, only 25 per cent of the bromoacid is precipitated in the solid form. By using water-white distilled linseed fatty acids, obtained from Archer-Daniels-Midland Company, Minneapolis, Minnesota, the yield of solid bromoacid may be increased to 48–53 g.
6. The theoretical yield of the ethyl ester from 20 g. of pure

hexabromide is 8 g. Losses through recrystallization, distillation, etc., amount to approximately 50 per cent; hence the actual yield is about 4 g. of ester.

7. The by-product, insoluble in dioxane, is heptabromostearic acid. If the solution is yellow at this point, a small amount of decolorizing charcoal should be added.

8. The melting point varies with the rate of heating. Any uniform method of taking the melting point may be adopted. It has been found convenient to insert the capillary tube in the bath when the temperature is five degrees below the expected melting point, and then to raise the temperature one degree per minute.

9. The ester contains about 0.5 per cent of free fatty acid, and for some purposes this is not objectionable, particularly if the acid itself is desired. It is recommended, therefore, that this step be omitted where possible, since the yields, particularly from small batches, may be as low as 80 per cent of the crude ester used. In the absence of an alkaline wash centrifuging is not necessary, as water alone causes no emulsions to form.

10. Usually three washings are sufficient.

11. The ester is much more stable toward oxidation than the acid; it is recommended that the material be stored as the ester, and that the acid be prepared only for immediate use. The acid oxidizes to some extent under the best of conditions and, unlike the ester, cannot be distilled without some decomposition. It is for this reason that the constants are determined on the ester rather than on the acid.

3. Methods of Preparation

Linolenic acid is always obtained from natural sources, chiefly from the oils of various seeds, such as hemp seed,¹ walnut,² poppy seed,² cotton seed,² and, best of all, linseed.^{3, 4} The crude acid has been purified via the solid hexabromide, either directly,^{5, 6}

¹ Hazura, Monatsh. 8, 268 (1887).

² Hazura and Grüssner, Monatsh. 9, 204 (1888).

³ Hazura, Monatsh. 8, 158 (1887); Erdmann and Bedford, Ber. 42, 1328 (1909).

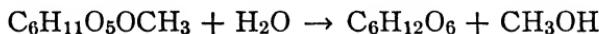
⁴ Erdmann, Z. physiol. Chem. 74, 180 (1911).

⁵ Erdmann and Bedford, Ber. 42, 1330 (1909).

⁶ Hazura, Monatsh. 8, 267 (1887).

or by hydrolysis of the methyl or ethyl ester, obtained by simultaneous debromination and esterification of hexabromostearic acid.^{5, 7} The method described above is a modification^{8, 9} of the procedure of Rollett.⁷

d-MANNOSE



Submitted by J. T. SHEEHAN and W. FREUDENBERG.

Checked by HOMER ADKINS, WINSTON WAYNE, and RICHARD JUDAY.

1. Procedure

A SOLUTION of 200 g. (1.03 moles) of α -methyl-*d*-mannoside (Org. Syn. Coll. Vol. 1, 1st Ed. (1932), p. 362; 2nd Ed. (1941), p. 371) in 3.2 l. of 2 *N* sulfuric acid (178 cc. concentrated sulfuric acid diluted to 3.2 l.) is steam-distilled from a 5-l. flask for one hour. The flask is heated externally during this time so that the volume of the solution remains constant. The mixture is transferred to a 2- or 3-gal. crock, 10 g. of decolorizing charcoal (Norite) is added, and the solution is rapidly stirred while it is neutralized (litmus) by the addition of barium carbonate (Note 1).

The mixture is filtered with suction through an asbestos mat supported on a filter paper in a 25-cm. Büchner funnel, and the barium sulfate is washed with two 100-cc. portions of water. The filtrate and washings are combined, and the clear colorless solution of the sugar is concentrated to about 300 cc. under reduced pressure (water pump) on a water bath whose temperature does not exceed 60°. The mixture is filtered, and the solid is washed on the filter with a little water. The combined filtrate and washings are then concentrated to a volume of 100 cc. under the conditions described above. The warm, slightly tan-colored syrup is poured into a 500-cc. Erlenmeyer flask. The transfer is com-

⁷ Rollett, Z. physiol. Chem. **62**, 422 (1909).

⁸ McCutcheon, Can. J. Research **B16**, 158 (1938).

⁹ McCutcheon, Can. J. Research **B18**, 231 (1940).

pleted by rinsing the distilling flask five times with 40-cc. portions of glacial acetic acid, each portion of the acetic acid being warmed to 50° in the bath before it is transferred. The acetic acid solution of the sugar is seeded with crystalline *d*-mannose (Note 2), and, after standing overnight at room temperature, the solution is placed in a refrigerator for a day or two.

The crystalline *d*-mannose is filtered and washed successively with two 20-cc. portions of cold glacial acetic acid, two 20-cc. portions of cold dry ethanol, and three 30-cc. portions of cold, dry ether (Note 3). After drying in the air for three days, the product weighs 112 to 115 g. (60 per cent of the theoretical amount) (Note 4) and melts at 126.5–127.5° (Note 5).

2. Notes

1. The calculated quantity of pure barium carbonate required to neutralize the sulfuric acid is 630 g. However, the checkers found that the mixture was still acid after stirring it for two to three hours with 780 g. of carbonate. An additional 100 g. of carbonate was required to bring the mixture to the neutral point. The checkers found that it was preferable to add 975 g. of barium hydroxide $[\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}]$, stir for one-half hour, and then to complete the neutralization by stirring with 75 g. of barium carbonate.

2. Crystallization may be induced by scratching with a glass rod if crystalline *d*-mannose is not available.

3. The sugar should be ground with each portion of the wash liquid, if the maximum purification with the minimum amount of solvent is to be obtained.

4. The submitters obtained 18–19 g. of crystalline *d*-mannose from the mother liquors, which increased the yield to about 70 per cent of the theoretical amount.

5. The sugar so prepared is said to be predominately α -*d*-mannose. If a purer product is desired, the substance may be recrystallized from 80 per cent ethyl alcohol. This procedure gives a product which melts at 131–132°; $\alpha_D^{23}, +15^\circ$. The recovery in this crystallization is about 80 per cent.

3. Methods of Preparation

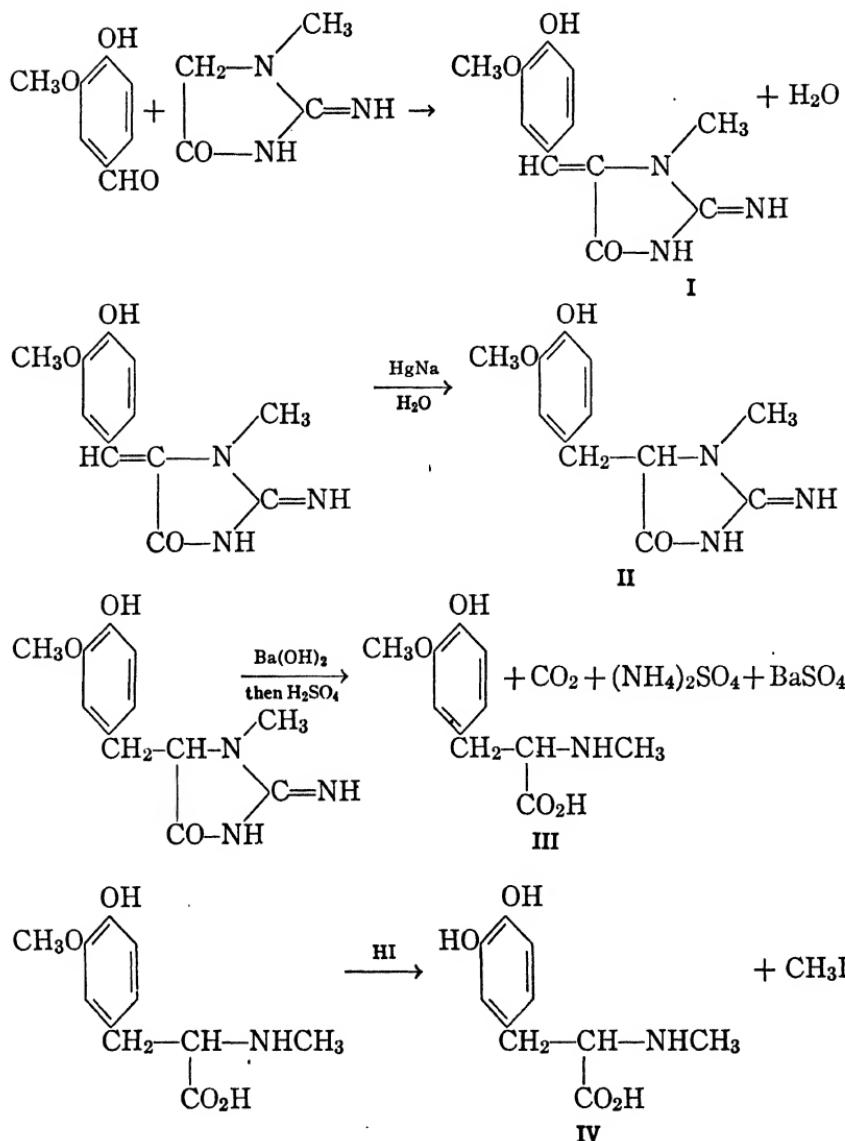
d-Mannose has been prepared by hydrolysis of the mannan in vegetable ivory,¹ but the crystalline sugar is apparently best obtained from mannan through the isolation of α -methyl-*d*-mannoside.² The method described above is similar to that of Hudson and Jackson² except that sulfuric acid, rather than hydrochloric acid, is used for hydrolysis of the α -methyl-*d*-mannoside. Levene³ has described what is probably the best method for the conversion of mannan to *d*-mannose without the isolation of α -methyl mannoside. The *d*-mannose obtained by Levene was predominately the β -isomer.

¹ Hudson and Sawyer, J. Am. Chem. Soc. **39**, 470 (1917).

² Hudson and Jackson, J. Am. Chem. Soc. **56**, 958 (1934).

³ Levene, J. Biol. Chem. **108**, 419 (1935).

N-METHYL-3,4-DIHYDROXYPHENYLALANINE

(Alanine, β -(3,4-dihydroxyphenyl)-N-methyl-)

Submitted by V. DEULOFEU and T. J. GUERRERO.

Checked by HOMER ADKINS, HAROLD H. GELLER, and EVERETT E. BOWDEN.

1. Procedure

(A) *5-(3-Methoxy-4-hydroxybenzal)-creatinine (I).*—In a large Pyrex test tube (51 mm. outside diameter and 200 mm. long) is placed an intimate mixture of 11.3 g. (0.1 mole) of creatinine (Org. Syn. Coll. Vol. 1, 1st Ed. (1932), p. 166; 2nd Ed. (1941), p. 172) and 24 g. (0.16 mole) of vanillin. The tube is placed in an oil bath, which is then heated to 170°, and the mixture is melted while it is constantly agitated (Note 1). The temperature of the mixture reaches 155° in about ten minutes; reaction then begins, and water is evolved. After three to five minutes longer, evolution of water ceases, and the mixture solidifies. The tube is heated for three minutes more, and then it is removed from the bath and allowed to cool.

When the temperature has fallen to 50–60°, 50 cc. of ethyl alcohol is added and the mixture is heated gently by occasional immersion in the warm oil bath. The solid partially disintegrates and forms a suspension. The suspension is filtered, and the solid remaining in the tube is warmed with a second 50-cc. portion of alcohol. This operation is repeated until all the orange-colored condensation product has been transferred to the filter. The material on the filter is then washed with three successive 30-cc. portions of water at 60°.

After drying, the crude product weighs 24 g. (95 per cent of the theoretical amount), melts at 261–263°, and is suitable for use in the next step. A pure product, which melts at 273°, may be obtained by recrystallizing the crude material from acetic acid.

(B) *5-(3-Methoxy-4-hydroxybenzyl)-creatinine (II).*—To a suspension of 24 g. (0.1 mole) of the crude condensation product in 150 cc. of water, contained in a 500-cc. beaker there is added, with continuous agitation, 180 g. of 3 per cent sodium amalgam (Note 2). The amalgam is added in six portions, at intervals of five minutes. The solid dissolves, and the initial orange-red color of the solution slowly fades as the reduction proceeds. With good agitation, decolorization is complete in forty-five to sixty minutes, if the starting material is pure. When the crude condensation product is used, the color of the solution fades to a

faint, but permanent, yellow tint, which should mark the end point of the reduction.

The solution is decanted from the mercury and filtered from suspended impurities. The filtrate is stirred and is acidified with hydrochloric acid to *pH* 6.6, using phenol red as the indicator (Note 3). After standing for two hours at 0°, the mixture is filtered and the solid is washed with a little cold water and dried. The product (free base) is microcrystalline, weighs 17.5–18 g. (72–74 per cent of the theoretical amount), and usually melts at 167–169° (Note 4). After solidification from fusion, the substance melts at 226–228°. When recrystallized from water, the substance melts at 231–233°. The crude product may be used for the subsequent hydrolysis.

(C) *N*-Methyl-(3-methoxy-4-hydroxyphenyl)-alanine (III).—In a 2-l. round-bottomed flask (Note 5), 18 g. (0.07 mole) of the crude reduction product is refluxed for twelve hours with a solution of 180 g. of crystalline barium hydroxide in 270 cc. of water. The hot solution is diluted with 1.2 l. of water, and the barium is precipitated by addition of 250–270 cc. of 6 *N* sulfuric acid (Note 6). The precipitated barium sulfate is separated by centrifuging and washed with two 100-cc. portions of water; the combined water solutions are evaporated under reduced pressure at 50° to a volume of about 50 cc. The acid solution is made alkaline to litmus by addition of about 10 cc. of a 12 per cent solution of ammonium hydroxide in water. After standing for twenty-four hours at 0°, the mixture is filtered, and the solid is washed with cold water and dried. The yield is 12 g. (74 per cent of the theoretical amount) (Note 7). On rapid heating, the solid melts at 273–275°. When recrystallized from water, the substance melts at 276–278°. The crude product may be used for the next step.

(D) *N*-Methyl-3,4-dihydroxyphenylalanine (IV).—In a carbon dioxide atmosphere, 12 g. (0.05 mole) of the methoxy compound is boiled gently for three hours with 24 g. of red phosphorus and a mixture of 60 cc. of acetic anhydride and 60 cc. of hydriodic acid (sp. gr. 1.7). The phosphorus is then removed by filtration and washed with 25 cc. of 50 per cent acetic acid. The filtrates are combined and, in a current of carbon dioxide, are evaporated to a

syrup at 50° under 35 mm. pressure. A 60-cc. portion of warm water is then added, and the solution is evaporated as before. The residue is dissolved in 100 cc. of water, and dilute ammonia (10 per cent by volume) is added until the solution does not change Congo red paper to blue (Note 8). The mixture is allowed to stand for two hours at 0°, and then the white crystalline precipitate is filtered. The precipitate is washed on the funnel with a little water containing sulfur dioxide, and is dried by washing with alcohol and ether. The product weighs 9.5 g. (82 per cent of the theoretical amount). When slowly heated it becomes slightly brown at 230° and melts at 282–283°; when rapidly heated it becomes slightly brown at 255–260° and melts at 290–292°.

This material may be purified by boiling 1 g. of it with 50 cc. of water containing sulfur dioxide, filtering the solution, and keeping the filtrate at 0° for twenty-four hours. The purified product (0.74 g.), when slowly heated, becomes slightly brown at 245° and melts at 287°; when rapidly heated it becomes slightly brown at 260° and melts at 298–300°.

2. Notes

1. Sometimes the evolution of water is too rapid, and there is excessive foaming. The reaction may be moderated by removing the tube from the oil bath.

2. The amalgam may be made by adding 5-mm. cubes of sodium (5.4 g.) to 175 g. of mercury, warmed to 30–40°, and contained in a mortar or Erlenmeyer flask. The mortar is covered with an asbestos board having a small hole in the center. The cubes of sodium are fixed on the end of a pointed glass rod and are quickly pushed through this hole beneath the surface of the mercury. A more convenient method is described in Fieser, *Experiments in Organic Chemistry*, 2nd Ed., 1941, D. C. Heath and Company, New York, p. 419.

3. The solution becomes dark in color if allowed to stand overnight.

4. In some cases the melting point may be as low as 98°; but after melting and solidifying, the substance melts at 226–228°.

5. A large flask should be used, since the mixture foams during the hydrolysis.

6. An excess of acid must be added to make certain that all the amino acid is in solution.

7. The yield can be increased slightly by evaporation of the mother liquor.

8. If the solution is made too alkaline, colored impurities precipitate. Neutralization must be performed carefully since the end point to Congo red is reached just before the colored impurities precipitate.

3. Methods of Preparation

5-(3-Methoxy-4-hydroxybenzal)-creatinine was first prepared by a similar method by Richardson, Welch, and Calvert.¹

N-Methyl-3,4-dihydroxyphenylalanine has been prepared by methylation of α -acetamino-3,4-methylenedioxycinnamic acid, followed by reduction and hydrolysis of the product;² and by a method similar to that outlined above.³

N-Methylaminoaromatic acids have been prepared by a variety of methods: by the reaction between methylamine and an α -bromo acid;⁴ by condensing methylhydantoin with aromatic aldehydes;⁵ by condensation of creatinine⁶ or benzoylmethylsarcosine with aromatic aldehydes;⁷ by methylation of the toluenesulfonyl derivative of the amino acid;⁸ and by substituting methylamine for ammonia in the Strecker synthesis.⁹

¹ Richardson, Welch, and Calvert, J. Am. Chem. Soc. **51**, 3075 (1929).

² Heard, Biochem. J. **27**, 54 (1933).

³ Guerrero and Deulofeu, Ber. **70**, 947 (1937).

⁴ Friedmann and Gutmann, Biochem. Z. **27**, 491 (1910).

⁵ Johnson and Nicolet, Am. Chem. J. **47**, 459 (1912).

⁶ Nicolet and Campbell, J. Am. Chem. Soc. **50**, 1155 (1928); Deulofeu and Mendivelzua, Ber. **68**, 783 (1935).

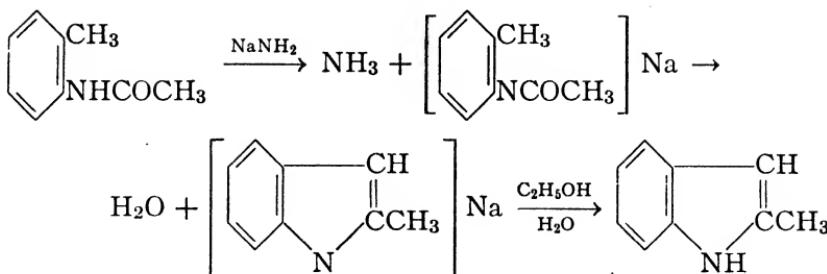
⁷ Deulofeu, Ber. **67**, 1542 (1934).

⁸ Fischer and Lipschitz, Ber. **48**, 360 (1915).

⁹ Kanewskaja, J. prakt. Chem. (2) **124**, 48 (1929).

2-METHYLINDOLE

(Indole, 2-methyl-)



Submitted by C. F. H. ALLEN and JAMES VAN ALLAN.

Checked by NATHAN L. DRAKE and RICHARD TOLLEFSON.

1. Procedure

IN a 1-l. Claisen flask is placed a mixture of 64 g. of finely divided sodium amide (Org. Syn. **20**, 86) (Note 1) and 100 g. of acetyl-*o*-toluidine (Note 2). About 50 cc. of dry ether is added (Note 3), and the apparatus is swept out with dry nitrogen. Then, with a slow current of nitrogen passing through the mixture, the reaction flask (Note 4) is heated in a metal bath (Note 5). The temperature is raised to 240–260° over a thirty-minute period and is maintained in this range for ten minutes. A vigorous evolution of gas occurs, the cessation of which indicates that the reaction is complete (Note 6). The metal bath is removed, the flask is allowed to cool, and 50 cc. of 95 per cent ethyl alcohol and 250 cc. of warm (ca. 50°) water are added, successively, to the reaction mixture. The decomposition of the sodium derivative of 2-methylindole, and of any excess sodium amide, is completed by warming the mixture gently with a Bunsen burner. The cooled reaction mixture is extracted with two 200-cc. portions of ether (Note 7). The combined ether extracts are filtered, and the filtrate is concentrated to about 125 cc. The solution is then transferred to a 250-cc. modified Claisen flask (p. 11; Org. Syn. Coll. Vol. **1**, 1st Ed. (1932), p. 125; 2nd Ed. (1941), p. 130)

and distilled. The 2-methylindole distils at 119–126°/3–4 mm. as a water-white liquid, which rapidly solidifies in the receiver to a white crystalline mass. This product melts at 56–57°. The yield is 70–72 g. (80–83 per cent of the theoretical amount) (Note 8).

The product may be further purified by dissolving it in 100 cc. of methanol, adding 30 cc. of water, and allowing the solution to stand in the ice chest for five hours. The pure white plates (52 g.) melt at 59°. An additional 10 g. may be recovered by cooling the filtrate after it has been diluted with about 20 cc. of water.

2. Notes

1. The sodium amide was ground in an open mortar, and at no time was difficulty experienced. As a precautionary measure, the grinding could be carried out under ether.

2. Acetyl-*o*-toluidine, m.p. 110–111°, obtained from the Eastman Kodak Company, was used. After the reactants are introduced into the flask, they should be mixed thoroughly with a long spatula.

3. The ether is added to facilitate the formation of the sodium salt of the amide.

4. It is advisable to cover the bottom of the reaction flask with soot, to prevent the metal from adhering to the glass.

5. Sand and salt baths are not satisfactory.

6. Reaction begins when the bath temperature has risen to approximately 200°. Frothing occurs, and the froth solidifies. The checkers found it necessary to stir the solidified froth into the reaction mixture, so that heating of the whole mass could be uniform. This stirring is necessary throughout—i.e., from the beginning of vigorous gas evolution until completion of the period of heating.

7. The indole may be isolated, less conveniently, by steam distillation; the crystalline product (m.p. about 56–57°) can be filtered from the cold distillate.

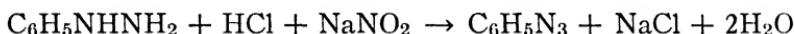
8. The method described here is of general application to substituted acetyl- and benzoyl-*o*-toluidines.

3. Methods of Preparation

2-Methylindole has been prepared, in very small yields, by distilling acetyl-*o*-toluidine with zinc dust,¹ and in better yields by heating the toluidide with sodium ethoxide or with barium oxide in a current of hydrogen at 360–380°.² The method described here has been used for the synthesis of substances related to physostigmine³ and is a modification of Verley's procedure.⁴

PHENYL AZIDE

(Benzene, triazo-)



Submitted by R. O. LINDSAY and C. F. H. ALLEN.

Checked by R. L. SHRINER and J. C. LAWLER.

1. Procedure

IN a 1-l. three-necked flask fitted with a stirrer, a thermometer, and a dropping funnel are placed 300 cc. of water and 55.5 cc. of concentrated hydrochloric acid. The flask is surrounded by an ice-salt bath, the stirrer is started, and 33.5 g. (0.31 mole) of phenylhydrazine (Note 1) is added dropwise (five to ten minutes is required). Phenylhydrazine hydrochloride separates as fine white plates. Stirring is continued and, after the temperature has fallen to 0°, 100 cc. of ether is added, after which a previously prepared solution of 25 g. of technical sodium nitrite in 30 cc. of water is added from the dropping funnel at such a rate that the temperature *never* rises above 5°. This requires twenty-five to thirty minutes.

The reaction mixture is subjected to steam distillation until about 400 cc. of distillate is obtained. The ether layer is removed

¹ Mauthner and Suida, Monatsh. **7**, 230, 237 (1886).

² Madelung, Ger. pat. 262,327 [Frdl. **11**, 278 (1912–1914)]; Ber. **45**, 1128 (1912).

³ Salway, J. Chem. Soc. **103**, 351 (1913).

⁴ Verley, Bull. soc. chim. (4) **35**, 1039 (1924).

from the distillate, and the aqueous layer is extracted once with 25 cc. of ether. The combined ethereal solutions are dried over 10 g. of anhydrous calcium chloride. The dried solution is placed in a 200-cc. ordinary Claisen flask arranged for vacuum distillation. *The flask must be surrounded by a cylindrical wire screen, and a laminated glass screen must be interposed between the operator and the apparatus* (Note 2). The flask is immersed in a water bath at 25–30°, and the ether is removed under reduced pressure. Then the temperature of the water bath is raised to 60–65°, and the product is distilled *in vacuo*. Phenyl azide boils at 49–50° at 5 mm. (Note 3). A yield of 24–25 g. (65–68 per cent of the theoretical amount) of the pungent, pale yellow, oily azide is obtained (Note 4).

2. Notes

1. The phenylhydrazine used was the best grade supplied by the Eastman Kodak Company. With technical material, or a preparation that was appreciably discolored, the yield was much less (45–50 per cent), and a considerable amount of tar was formed.

2. Care must be exercised during the distillation. Phenyl azide explodes when heated at ordinary pressure, and occasionally at lower pressures. The water-bath temperature should never be permitted to rise above 80° at any time.

3. Phenyl azide boils at 66–68°/21 mm. with a bath temperature of 70–75°. It is advisable to use as low a bath temperature as possible and a pressure of 5 mm. or less. The checkers have used these directions repeatedly without any explosions.

4. The product should be stored in a brown glass bottle. It will keep for a month in a cool, dark place.

3. Methods of Preparation

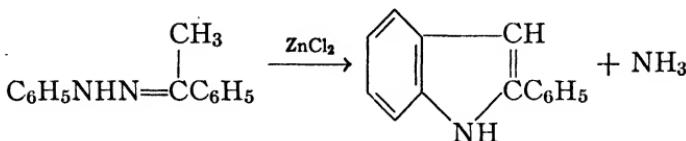
Phenyl azide has been prepared by the action of nitrous acid upon phenylhydrazine hydrochloride;¹ of ammonia upon diazo-

¹ Dimroth, Ber. 35, 1032 (1902).

benzene perbromide;² and by the reaction between a diazo salt and sodium azide,³ or hydroxylamine.⁴

2-PHENYLINDOLE

(Indole, 2-phenyl-)



Submitted by R. L. SHRINER, W. C. ASHLEY, and E. WELCH.

Checked by HOMER ADKINS, ALAN K. ROEBUCK, and HARRY COONRADT.

1. Procedure

IN a tall 1-l. beaker is placed an intimate mixture of 53 g. (0.25 mole) of freshly prepared acetophenonephenylhydrazone (Note 1) and 250 g. of powdered anhydrous zinc chloride (Note 2). The beaker is immersed in an oil bath at 170°, and the mixture is stirred vigorously by hand. The mass becomes liquid after three to four minutes, and evolution of white fumes begins. The beaker is removed from the bath and the mixture is stirred for five minutes. In order to prevent solidification to a hard mass, 200 g. of clean sand is thoroughly stirred into the reaction mixture. The zinc chloride is dissolved by digesting the mixture overnight on the steam cone with 800 cc. of water and 25 cc. of concentrated hydrochloric acid (sp. gr. about 1.2). The sand and crude 2-phenylindole are removed by filtration, and the solids are boiled with 600 cc. of 95 per cent alcohol. The hot mixture is decolorized with Norite and filtered through a hot 10-cm. Büchner funnel, and the sand and Norite are washed with 75 cc. of hot

² Griess, Ann. 137, 68 (1866).

³ Nöting, Ber. 26, 86 (1893).

⁴ Fischer, Ann. 190, 96 (1877); Mai, Ber. 25, 372 (1892); 26, 1271 (1893); Forster and Fierz, J. Chem. Soc. 91, 855, 1350 (1907).

alcohol. After the combined filtrates are cooled to room temperature, the 2-phenylindole is collected on a 10-cm. Büchner funnel and washed three times with small amounts (15–20 cc.) of cold alcohol. The first crop is quite pure; after drying in a vacuum desiccator over calcium chloride it weighs 30–33 g. and melts at 188–189° (corr.) (Notes 3 and 4).

A little Norite is added to the combined filtrate and washings, which are then concentrated to a volume of 200 cc. and filtered. The filtrate, on cooling, deposits a second crop of 5–6 g. (Note 5) of impure product, which melts at 186–188°. The total yield of 2-phenylindole is 35–39 g. (72–80 per cent of the theoretical amount).

2. Notes

1. Acetophenonephenylhydrazone is prepared¹ by warming a mixture of 40 g. (0.33 mole) of acetophenone and 36 g. (0.33 mole) of phenylhydrazine on the steam cone for one hour. The hot mixture is dissolved in 80 cc. of 95 per cent alcohol, and crystallization is induced by agitation. The mixture is then cooled in an ice bath, and the product is removed and washed with 25 cc. of alcohol. There is obtained 54–57 g. of white product. A second crop of 4–10 g. is obtained by concentrating the combined filtrate and washings. The combined solids are dried under reduced pressure, over calcium chloride, for a half hour. The total yield of acetophenonephenylhydrazone, m.p., 105–106°, is 61–64 g. (87–91 per cent of the theoretical amount).

2. It has been reported² that such a large amount of zinc chloride is not necessary, but the submitters found that equal parts of acetophenonephenylhydrazone and zinc chloride gave lower yields.

3. Using 3.2 times the quantities specified above, except that no sand was added in separating the product, the checkers have obtained yields of 75–80 per cent of 2-phenylindole.

4. While drying, the surface of the product becomes very light green in color.

¹ Reisenegger, Ber. **16**, 662 (1883).

² Arbuzov and Tichvinshi, J. Russ. Phys. Chem. Soc. **45**, 70 (1913); [C. A. **7**, 2225, 3599 (1913)].

5. The filtrate still contains some 2-phenylindole, but great difficulty is encountered in trying to purify the crude material.

3. Methods of Preparation

2-Phenylindole has been prepared by heating benzoyl-*o*-toluidine in an atmosphere of hydrogen,³ the reaction being improved by the use of sodium amyloxide as the condensing agent; by heating phenylacetaldehydophenylhydrazone with five parts of anhydrous zinc chloride;⁴ by warming phenacylbromide with 2 moles of aniline;⁵ by elimination of a molecule of water from *o*-aminodesoxybenzoin,⁶ a compound prepared from *o*-nitrodesoxybenzoin; by dehydrogenation of benzal-*o*-toluidine;⁷ and by action of anhydrous zinc chloride upon the phenylhydrazone of acetophenone.⁸

³ Madelung, Ber. **45**, 1131 (1912).

⁴ Fischer and Schmitt, Ber. **21**, 1072 (1888).

⁵ Mohlau, Ber. **15**, 2480 (1882); Bischler, Ber. **25**, 2860 (1892).

⁶ Pictet, Ber. **19**, 1064 (1886).

⁷ Etard, Compt. rend. **95**, 730 (1882).

⁸ Fischer, Ann. **236**, 133 (1886).

ADDITION AND CORRECTION FOR
PRECEDING VOLUME *

Dimethylethynylcarbinol (Org. Syn. 20, 40):

A general method has been published¹ for preparation of ethynylcarbinols, which is simpler than the method cited and which gives better yields. Yields of dimethylethynylcarbinol as high as 80 per cent have frequently been obtained.² The reaction flask is immersed in a Dry Ice bath while the acetone is added, and acetylene gas is passed through the mixture throughout the course of the reaction.

KENNETH N. CAMPBELL, private communication:

* The usual section devoted to later references to preparations in the preceding volumes has been omitted from the present volume. This material will be included in Collective Volume II, covering Volumes X-XIX, which is scheduled to appear in 1942.

¹ Campbell, Campbell, and Eby, J. Am. Chem. Soc. **60**, 2882 (1938).

² Froning and Hennion, J. Am. Chem. Soc. **62**, 654 (1940).

SUBJECT INDEX

(This cumulative Index comprises material from Volumes 20 through 22 of this series; for previous volumes see Collective Volumes I and II.)

Names in small capital letters refer to the titles of individual preparations. A number in ordinary bold-face type denotes the volume. A number in bold-face italics refers to a page which gives preparative directions for substances formed either as principal products or as by-products; numbers in ordinary type indicate pages on which a compound or a subject is mentioned in connection with other preparations. For example, ACETONE CYANOHYDRIN, 20, 42, 43, indicates that acetone cyanohydrin is mentioned on page 42 and that directions for its preparation are given in detail on page 43 of Volume 20.

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